What's my Diagnosis?

Physician Panel Discussion Based on the Community Panel Presentations

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[00:00:05] **Dr. Benjamin Greenberg:** I'm gonna invite Carlos and Michael and Tammy, Leslie and Dean to come join me on stage and to grab a seat. What we want to do is really integrate what you heard, from the individual perspective, the individuals who've been afflicted by these conditions and what their journey is and now take it from the clinical side. A lot of folks have a very challenging journey getting to a diagnosis. There are a lot of misdiagnoses and a lot of delayed diagnoses, and sometimes titles change. So, we want to walk everybody through that.

[00:00:39] As everybody's joining us on stage, I'll remind those of you who are online and watching virtually, we're glad you're here. There is a way to ask questions online. There should be a question and answer or chat box. You can ask the question, and we have individuals here who can interrupt and ask on your behalf. So, please feel free to send those questions in.

[00:01:04] So, we got the crowd. Now, they have no idea what I'm going to ask them. This is the best part. And so, they don't know what to expect. But since Carlos is sitting closest and has been one of my mentors and friends now for a very long time, who was part of the original group at Hopkins forming the first transverse myelitis center, I'm actually going to start at a high level with you, Carlos. Just to give everybody in the audience a sense of the historical arc and what you consider to be in the rare neurologic disorders over the last 20 years, 25 years, what were the, what you would consider the biggest changes in our approach to diagnosis? What do we do differently now than we did when I was a resident that you think has been meaningful to getting people to an accurate diagnosis and understanding these conditions?

[00:01:58] **Dr. Carlos A. Pardo:** How much time do I have?

[00:02:00] **Dr. Benjamin Greenberg:** You have 30 seconds. Ready? Go. No.

[00:02:05] **Dr. Carlos A. Pardo:** Well, thank you so much for the organization of this meeting, and thank you to Angela, Ashley, Andrews, Andreas, and Lyd, four A's and one L. So, thank you for sharing your stories with us. The journey that is bringing us to this day here. Where is Doug? He disappeared. He always disappears.

[00:02:32] **Dr. Benjamin Greenberg:** He always disappears.

[00:02:33] **Dr. Carlos A. Pardo:** So, you need to understand something that is very interesting from historical point of view. As you can hear very well, my Spanglish is getting better, despite being here for a long time. But I had basically one of my classmates in residency, Doug Kerr, who back in the late '90s, came with the idea, hey, we need to study this disorder that's called transverse myelitis because I have no idea what it is. And I said, doc, well let's sit down and talk about that. And then with the help of Sandy, we got basically in the challenge to organize idea about how to understand what transverse myelitis is and how to tackle the issue of transverse myelitis in our patients.

[00:03:21] At that time during our residency training in the '90s, basically we had a tiny bit of an idea about transverse myelitis. Transverse myelitis actually was in the basket of multiple sclerosis, and many patients with transverse myelitis actually were diagnosed erroneously as multiple sclerosis and were treated as multiple sclerosis. But many things in the '90s actually, many of these neuroimmunological disorders had the same treatment, IV steroid treatment, and steroids and steroids and steroids. And at the end we end up basically treating some patients correctly, some patients probably incorrectly. But the bottom line is from that time when we started digging in the issues of transverse myelitis, understanding transverse myelitis better, we basically encountered really a complexity of the disorder.

[00:04:15] I think that has been a revolution in terms of understanding these problems is: number one is, we were able to guide a lot of patients with transverse myelitis back in the late '90s, we were able to have a much better idea what was the meaning of transverse myelitis. In other words, when you see a patient, you see one patient. When you see 10 patients, you see a little bit of difference between patient and patient. When you see 100 patients, you can see the spectrum and the variability of the disease. So, what we had basically is a great effort because, thank you to getting all of patients together, we were able to characterize much, much better what was the meaning of transverse myelitis. In 2002, we sat down for the first time and among many colleagues, not only from Hopkins, but also from Mayo Clinic, from other institutions around the country, we sat down to discuss, ok, why we are going to call transverse myelitis, and that was the criteria that was generated at that time.

[00:05:22] But it's quite amazing because in 2005, our colleagues at the Mayo Clinic discovered that one of the disorders that we had called transverse myelitis was basically associated with an antibody that was aquaporin-4 and that basically opened a revolution in understanding inflammatory disorders. And since then, we are seeing MOG, we are seeing other type of immunological disorders that have been very well characterized to understand the concept of transverse myelitis.

[00:05:51] So, at this moment what we have historically is a great progress, and this is not because everybody is basically diagnosed with one disease. We have been, in many ways, taking all of the spectrum of these spinal cord disorders that are associated with inflammation and trying to dissect and understand what the cause and the clinical phenomenology. But there is one thing that is very important. I think that was Andrew who was talking about hiccups, and was talking about nausea. And it's very amazing because that is actually one of the clinical phenotypes of patients with neuromyelitis optica. We learned about that when we saw a 100, or more than a 100, patients with that spectrum, and the clinician were able to say, ok, now I understand that when a patient show up in clinic with concerns about hiccups and concerns about something like nausea, vomiting, we need to think about NMO, or we need to think about MOG when patients are showing up with bilateral optic neuritis.

[00:07:01] So, all of that is something that we have learned in the past 20 years. But it's important because it's based on what you have contributed and many patients and family have contributed. I mean, there is no such of a beautiful science of medicine. There is no medicine if there are no good communication between patients and researchers and physicians. So, that is the value of all of you coming here, interacting with us,

and we try to understand what is going on. So, going to finish, but the most important part is one thing that I always emphasize, and actually we have outlined this very clearly.

[00:07:42] As you heard from our patients here in the panel, the critical part for understanding a disease is a good communication. So, if you are not able to discuss with your healthcare provider very well what is going on, we are going to be lost in the picture. And the reason is the diagnosis of neurological diseases, particularly this type of diseases, is not based in MRIs. It's not based in the spinal tap. It's based in the understanding what has been the evolution of symptoms. The understanding what is going on with every patient. And that clinician basically needs to take care of that information to outline and put together the pieces of information that are going to give a final diagnosis. One thing that we always teach the residents is, you need to sit down and spend time with your patients to understand what is going on before you order an MRI because that is critical. And understanding what is going on in that clinical picture is basically going to provide many of those flavors that these type of inflammatory disorders that are relatively rare may produce in terms of symptoms in patients and the clinical profile of patients. I'll stop here.

[00:09:02] **Dr. Benjamin Greenberg:** No, it's a good answer and you bring up a lot of topics. So, when I was an undergrad, I was actually a, my major was history. That was, I wasn't a biology major, I was a history major, so I appreciate the historical context. And there's a couple points I wanna pull out before, Dean, you're going to be on the hot seat next just to mentally get ready. So going back, literally to the 1890s, with one of the founders of the Hopkins Hospital, Sir William Osler, he would teach his students, the quote was, "Listen to your patients. They're telling you everything you need to know to make a diagnosis."

[00:09:36] Now, importantly, that's the 1890s. And when you look at neurology, at that point in time, the field of neurology has been one of phenomenology. We look for patterns as a neurologist either by listening to our patient or by doing an exam and we would focus on where is the problem. Is it your brain? Is it your spinal cord? Is it your nerve? Is it your muscle? And even to this day, that's how we teach our residents to what we call localize the lesion, find where the problem is. And then once we know where the problem is, we then ask what's the problem, what caused the damage. And you made a reference to when the myelitis organization began and a focus on myelitis that a lot of our patients were hearing the term multiple sclerosis. So, just as a fun little exercise for everyone here, either you or your loved one who went through this journey, at some point in your diagnostic journey, how many people here had the term multiple sclerosis brought up as part of the diagnosis? I'm going to estimate at least half of the hands here. And it's because we were, that was the known disorder to affect the brain and the spinal cord and the optic nerves. That's the one we knew and we've known about it for over 150 years.

[00:10:51] So, in 1999, Dean, you and Brian Weinshenker and others, published a paper around neuromyelitis optica. And the approach you took was an interesting one, and I picked 99 for a reason. It's before we had a blood test to separate out neuromyelitis optica. And the approach you took was by looking at response to therapy as a way to differentiate neuromyelitis optica and multiple sclerosis. There was an attempt to say, this is a distinct disorder and it's distinct for a lot of reasons.

[00:11:23] I want to ask about your experience then. What was it, in terms of the patients, that you were seeing, that you were learning from patients that made you committed to separating it out as a separate entity? And then if you would just comment on the subsequent work that came out, the identification of the aquaporin-4 antibody, and how you think that's changed the way we practice, and what it means for patients.

[00:11:53] **Dr. Dean Wingerchuk:** I'll try. Thanks, Ben. So, first of all, thanks to everybody today that shared their stories as well. That was inspiring, and I'm grateful to be a part of the meeting. So, way back in the mid-1990s, one of my mentors, Brian Weinshenker, who's attended this meeting, and many of you probably

know attended this meeting many times, suggested to me that we look into this disease that was called neuromyelitis optica or Devic's disease or Devic's syndrome, which at the time was considered an unusual restricted severe form of MS. And I remember him sort of teaching me that there are many examples in medicine where if you look at something that seems to be distinct and rare that might be a subset of something else, you can learn about the whole picture.

[00:12:53] And this appeared to be a good example because, at least, at that time, the people that had been diagnosed with NMO, a rare condition, of course, had been diagnosed with NMO at Mayo Clinic were, if you will, sort of the clearest examples of NMO. There was little to no overlap between their disease and typical multiple sclerosis. And so that's what we looked at. We looked at sort of the historical definition dating all the way back to the 19th century and allowed for some expansion of that, and that allowed us to realize that, yeah, there is this distinct group of patients, here are all the reasons, and we had built on work of others too, but here are all the reasons that they look different, their symptoms, their exam, their MRI's, their spinal taps, and their course over time. And one of the things we recognized was that historically, that was thought to be sort of a one and done kind of condition for most people that they would have an optic neuritis and myelitis attack and then nothing. But we found that actually most people went on to have more attacks.

[00:14:11] One thing that came out of that was building this group, or cohort of patients that we had characterized very carefully, and that allowed our group collectively when Dr. Lennon and her colleagues in the laboratory found this antibody pattern from blood tests, that allowed us to go back and look at people with typical MS and people that we had diagnosed with NMO and very quickly and very clearly showed that this antibody really only showed up in NMO. And that was a very nice example of sort of the correlation between the symptoms, the signs, the imaging, the pathology, and now this new biomarker.

[00:15:01] So that, as Dr. Pardo said, has opened up entirely new fields, and today, we have laboratories around the world who are kind of doing this in reverse. They're discovering antibodies and biomarkers all the time and then they're going back to the careful characterization of what's going on with patients and that's how now we have this whole field of so-called autoimmune neurology, where we're linking these biomarkers to the clinical syndromes. And it's part of the reason, I think you mentioned this earlier, that diagnoses are changing because that's progress. That's what progress means is that as we get smarter and as we discover new biomarkers and validate them, we'll advance the science.

[00:15:48] So, now we have treatments for NMO 20 years later, which is amazing to think that in about 15 years after the discovery of the antibody that we had multiple FDA approved treatments for this rare disease, all accelerated by this sort of careful building of each step of the science. And I think that's going to continue.

[00:16:10] **Dr. Benjamin Greenberg:** Yes. And I would just stress, I really, on that last statement, if you look around the world in rare diseases and you look for a disorder with the prevalence, the number of people in the world affected as is the prevalence for neuromyelitis optica, it's a very rare disease, to find another example of a condition with four FDA approved therapies is unheard of in the world of rare diseases. And we really have to trace back the history appropriately and it started with the recognition of this isn't a variant of MS, there is something different there. And starting with the clinical phenotype and then having a biomarker, a pathologic antibody found, it allowed the field to move forward in a very different way.

[00:16:53] So, I mean, it was really history making work that led to tremendous benefits for our patients and families. And we're on a similar journey, I think, now with another antibody associated disorder. Mike, I'm going to, pick on you for this one. So, in our clinics, we would have individuals who we would swear had

neuromyelitis optica. And we'd send the test to the Mayo Clinic, and they'd say negative for the aquaporin-4 antibody. And we'd say, there's something wrong with your test. You got to do better. And they try again, negative, negative, negative. But again, it was working from the phenotype and saying there's something here. And then we started to recognize there are some differences between them. And do you want to comment on the next antibody in line that shares such a clinical phenotype with neuromyelitis optica?

[00:17:47] **Dr. Michael Levy:** Don't worry, everybody. I'm not going to go on and on. I don't have quite the historical viewpoint as my colleagues here, but I will tell you that back in the 2015 era, before we had the MOG test, we had about 25% of our patients that were not testing positive for aquaporin-4. They were frustrating to us because we wanted to give them that certainty of a diagnosis. We couldn't do that. Then they weren't quite responding the same way to the treatments we were offering. And then these new antibody tests came out, as Dr. Wingerchuk mentioned, the next one on the line was the MOG antibody. And it was like suddenly, again, once the test was confirmed, it was effective. We started sending off all these samples, and it was like, oh, of course, you have MOG. You know, looking back, it's much more obvious. And then we could put these people together and say, ok, they don't respond to these medications. They do respond to these. And then, you know, pharma jumped right in. And now we have two international clinical trials going on in MOG. Again, very rare disease, maybe a little more common than NMOSD, but not much. And hopefully, we'll have two FDA approved drugs by 2026. So, this is the second, and there'll probably be a third, and a fourth, and many more.

[00:19:03] **Dr. Benjamin Greenberg:** Now that we have these tests, Tammy, I'm going to turn to you. I know you've spent time in the world of diagnostic testing and worked with Stacey Clardy and others in looking at cohorts of patients and then the operational characteristics of the tests. We heard from our patients, who've been through the journeys, MRI's, lumbar punctures, blood work, and a lot of head scratching for a certain period of time. Can you comment about the state of the art now in terms of your views on--as patients are seeking diagnoses or first presenting--what type of testing should we be doing in terms of the blood work and these other tests?

[00:19:45] And I say this and I want everyone to hear it. All of you in the room have been through the journey to some level, you or your loved one. And so, you may ask, well, I already have my diagnosis, why is this important? You are all Sandy ambassadors now in the world. We get more referrals and more recognition of conditions from you having a friend of a friend on Facebook post: I'm in the hospital and I can't see out of my right eye and they have no idea what's going on. And it's one of you now, that we've moved away from the kitchen phone to Facebook, who can proactively say, have they tested for fill-in-the-blank? And whether you wanted to be here or not, you are now consultants, medical consultants to the world. But it's an incredible gift that you can give to be aware of these things. So, if you were advising the world in terms of how to think about this test, I know it's a broad question, but can you give a context in terms of how people think about, what should be part of the armamentarium of testing?

[00:20:53] **Dr. Tammy Smith:** Yes, I'll give it a shot. First of all, I want to say I'm really humbled hearing everybody's stories and really appreciate the lengths you go to get answers from your physicians and all of the poking and prodding that you have to go through. Sometimes it does seem like we're just testing everything under the sun, and we can't get an answer for you. We want to find those answers, but I recognize that it's really challenging to go through multiple lumbar punctures or feeling like you have no more blood left to give that we're asking for more.

[00:21:27] So, my background is really in laboratory science. I'm a much less experienced clinician than the rest of these people on this stage. But I have years of experience working in labs before I became a neurologist.

And I'm really passionate about understanding the diagnostic testing and helping improve it, as well as helping communicate with both my colleagues, as well as patients, how to interpret the diagnostic testing.

[00:21:54] And really as far as state of the art, most of our laboratory testing, the AQP4 and the MOG testing. Right now, we recommend a cell-based assay, and that probably doesn't mean a lot to a lot of patients, but there are lots of different ways to perform any given test. So, when you see a result in your medical record with a big exclamation point that says it's positive and often when your less experienced clinicians see that too, they take it to mean the truth, that is a positive. And also when it says everything is negative, we take that to mean the truth. Okay, we've tested and they don't have that.

[00:22:33] But I think what we often forget is that every test has a particular level of sensitivity and very few tests are a 100% sensitive. So, that means that even if you have that antibody, sometimes that test will result negative. Ok. And then also every test has a specificity. So that's if you have that antibody, if you have that result be positive, how likely is it that it's the truth. Right? And, again, every test at every lab, even the same test performed in different labs will actually perform differently.

[00:23:11] So, I think it's just really important to communicate that with all of our patients and our providers to know where your diagnostic testing was done and how it was performed to help inform the interpretation. And everyone loves a black-and-white result on a computer, but as everyone else here has already said on this stage, what really matters is how our patients present it. Right? What are their clinical symptoms? What are they experiencing? And then additional imaging from a neurologic exam, from imaging, and laboratory testing working together. So, as far as state of the art, I mean, I can nerd out on like how to do the test the most sensitive versus the most specific in different labs? But really, the state of the art is putting all of the information together, talking to our patients, getting their history, performing an excellent neurologic exam, looking at the imaging findings, response to therapy, and then using the diagnostic testing to help inform our interpretation of that.

[00:24:16] **Dr. Benjamin Greenberg:** You shouldn't panic, but the takeaway is sometimes the test is wrong. That's a short version, but it's always a question than a percents. For a lot of the tests, it's rarely wrong. There's not this thing that's 100%. There are some tests that we can look at. If the test is of a certain abnormality, we can say the likelihood of this being wrong is extremely low. There are other tests where the performance isn't the same. I think the world where we're struggling with this the most right now is in the world of anti-MOG associated disorders where depending on the clinical situation or depending on the level of abnormality. We're still trying to understand the implication for the test, which is different than with the aquaporin-4 antibody.

[00:25:02] And so, where you ended, I think, is extremely important, and that is we have to take the whole picture together. We have one individual who shared your story and, when I asked her diagnosis, she said double seronegative NMO. And I understand, but I hate that terminology. It's like, I have NMO, but these people can't figure out their testing. So, I'm just kind of in this category. And it is around test performance and characteristics and when the test is sent. We have sometimes sent blood tests on patients right after they had plasmapheresis or steroids and got a negative, but it was the impact of the therapy. So, it's not just the situation or the testing, but the timing. So in the end, even though biology and understanding the molecular biology has done tremendous things for improving our ability to diagnose and treat patients, we still come back to the history of the physical and understanding what our patients are experiencing to try and give the most accurate diagnosis.

[00:26:02] And so then, the world threw us a little curve ball as we got to 2012 and 2014. And Leslie, I'm going to turn to you with this next part. And I'm going to have a little confessional for the moment. And I blame Carlos and Doug for this, just so we're all very, very clear. So, I had done my residency at Hopkins, my

fellowship. I was on faculty. I had been indoctrinated into the world of transverse myelitis. I had been taught by Carlos and Dean and Brian about the wonders of plasmapheresis, and we're going to hear about that later this morning. Ad pack up my bags and I go down to Dallas, Texas and, was fortunate, had a partner in crime here somewhere, Maureen Mealy is here, who came and, and set up the transverse myelitis program here in Dallas. And I walked around with my expert knowledge, seeing patients with transverse myelitis. And I knew what it was. You come in with sudden onset weakness and a spinal cord lesion and you look for inflammation and I need to dive in and treat the immune system.

[00:27:05] And then in 2009, literally the year I moved here, I had a whole series of cases at Children's that just didn't seem right. They were myelitis but there were differences among them. And I published what, to this date, is the worst titled paper in history, [audience laughing 00:27:25], "Transverse Myelitis Plus Syndrome." And, yes, what the hell was I thinking? Why would you let me do that? So, and what it showed, the confessional here, is we get ingrained during our training to think a certain way. We see it, we recognize it, and when something doesn't add up, my brain, our brains, have difficulty incorporating that information. And what I was seeing in 2009 and then 2012 and since then, at first I didn't realize, but it was a disorder that we now call acute flaccid myelitis. And it looked very much like traditional transverse myelitis with one big difference. Doug and Carlos had taught me for years that after myelitis, muscles got tight and everybody had spasticity. And I was seeing children at Dallas Children's, just down the street here, whose limbs were flaccid. And I was seeing kids where their arms were flaccid and their legs were tight. And I just, I couldn't make sense of it, until the spotlight got turned on acute flaccid myelitis.

[00:28:29] And I'm curious, Leslie, if you can comment about how, again from a diagnostic journey perspective, how acute flaccid myelitis works into this storyline of these different conditions and clinically or even radiographically, what it might share with some of these rare autoimmune disorders. So, how is it different and how is it similar?

[00:28:53] **Dr. Leslie Benson:** Sure. I have to admit, I think we read that paper and found it interesting at one point in time.

[00:28:58] **Dr. Benjamin Greenberg:** Yes. But you're all laughing behind my back, like, how did they get this title in?

[00:29:04] **Dr. Leslie Benson:** But, no. I mean, we similarly in 2008, saw a cluster of patients that we called polio-like myelitis because we didn't have that AFM label yet, but we didn't write a paper with a bad title.

[00:29:19] **Dr. Benjamin Greenberg:** It's fair.

[00:29:20] **Dr. Leslie Benson:** But then that did make 2014 sort of a like, wait a second, this feels similar experience. Like, all of a sudden, there's a bunch of kids who have arms that are flaccid that shouldn't. And so, again, felt like this was a polio-like myelitis, and it was 2014 when we saw the terminology start to harmonize into AFM so that we could be more clear and consistent across the community, the medical community. I still think we're in a place, though, where we don't, like I know what 2014, 2016, and 2018 AFM looked like, but there's that, I think we still, there's room to work on these. It's kind of like AFM…it's kind of like myelitis cases that still crop up occasionally.

[00:30:12] **Dr. Benjamin Greenberg:** AFM plus syndrome? Anybody? No? No takers? Help me out. Come on.

[00:30:19] **Dr. Leslie Benson:** In terms of the overlap, you know, certainly, MOG and AFM in that first week can look exactly the same. They can have an "H" sign on the MRI, like we call it. They can have very similar sudden

onset of weakness. They can have a recent fever and high inflammatory markers and really look very much the same from a workup perspective. And so it's we're being detectives and putting together the story that the family is telling us, the recent infections, the lab work, the MRI's, and then making a treatment decision in that those first days and following over time, is really what oftentimes ends up, whether the MOG comes back positive or how the symptoms evolve, that lead towards our best ability to label it with a diagnosis.

[00:31:12] **Dr. Benjamin Greenberg:** Yes. And one of the things that happened, even though there were cases being seen in 2009. 2012 there were reported cases. It wasn't until 2014 with Terry's group in Colorado where it was a cluster all at once. And I'm not going to break HIPAA, but you're waving your hand. You're part of the cluster, okay, that's self-identification. I didn't do it. But it was, if it's fair to say, Terry, the fact that there was a cluster, having multiple people in the hospital at the same time is a way to punch us in the face and say, it's not a plus syndrome, this is something unique.

[00:31:51] And the reason I make that point is in rare disorders, and AFM is a rare disorder. If you look at the prevalence, if you look at the incidence, it's a rare disorder, there is a tremendous power in numbers. So, the ability even for the medical and scientific field to recognize that there's something unique going on at a population level requires a certain number of patients to reach a critical mass for morons like myself to separate it out from a plus syndrome to its own entity. And it's not just true on the diagnostic side. So, throughout the entire patient journey, there is power in numbers as we sort out response to therapy, what works, what doesn't, and the continual sharing of your stories and your experiences and your data. And as Sandy and Chitra and GG send out surveys, they actually are meaningful. We look at the data. We learn from the data. We try and get better from the data, because we are only as good as the information you share and provide. We will not see a pattern until we see it enough times and it's obvious enough.

[00:32:59] So, what differentiates out, and Doug's not in the room so I can say this, he will self-admit when he started the Myelitis Center, he got a few years in, and I think he's publicly apologized to his first 50 patients, and I publicly apologize to my first 50 patients. The first 50 are always more valuable to us than we are to them because it takes about 50 to start seeing patterns. And now that we're in the area of rare diseases, often it takes larger numbers.

[00:33:29] As patients and families come to us in the very beginning, everybody is seeking a diagnosis, a title, because there's a feeling that until I have the accurate title, nothing else happens. And as clinicians, we rely on criteria to put people in the categories. So Dean, I'm gonna, ask you to comment on the journey. We'll start with NMO and we'll move to some others on how we think about, as we integrate all the history and all the testing and all the science, coming up with diagnostic criteria. And I'm not sure if you're in a position to give folks an update on the fact that we're continuing to evolve in diagnostic criteria and use neuromyelitis optica as an example. And if you're willing, even comment on some of the challenges of how we handle related conditions.

[00:34:16] **Dr. Dean Wingerchuk:** Sure. So, I've been fortunate with many colleagues to have participated in proposals of a number of different diagnostic criteria as they've evolved over the last 20-plus years, and the last time we did this was in 2015. There's a project underway now. We're calling it International Panel on NMOSD Diagnosis 2025 with some optimism that we might actually finish it next year. We'll see. But the idea is to try to refresh these criteria and update them to deal with advances in science, advances in knowledge in NMO itself, to provide guidance to doctors across the world, recognizing that not everybody, not all doctors, all patients have access to the antibody testing that makes such a big difference for these diagnoses.

[00:35:11] So, we're calling it a refreshing of the seropositive aquaporin-4 positive NMOSD diagnosis. But we're also trying to take the opportunity, I hope with this very large international collaboration, to have the

field rethink about how we approach these conditions and what we call them. I guess very simply I could say that the term NMO spectrum disorder, as helpful as that has been, since it was coined in 2007, has also led to some confusion. A lot of things under that umbrella that probably don't belong there or don't clearly belong there. One example of that, of course, would be MOGAD. Now we can carve that out as its own separate entity.

[00:36:06] But this project will hopefully, do both the clinical and the research fields a service by more clearly delineating what do we know and what do we need to know in the future? How do we get there? How do we define a roadmap, so that when we see you've heard everybody today speaking about the emphasis on how do people with these conditions present? What are the similarities and what are the differences as the condition evolves? How can we take that material, that information and formulate criteria for guidance for clinicians and for researchers so that we can discover the biomarkers that are attached to the specific clinical phenotypes as soon as possible? So that's kind of the overarching aim. Did I answer your question, Ben?

[00:36:58] **Dr. Benjamin Greenberg:** Yes. And we're going to have a dedicated session on diagnostic criteria, but I wanted people to get a sense of as we learn more from you and learn more for experiences, the criteria changes. And that can be awkward, because one day you're given one name, and the next day you come to my clinic and I say, just kidding. We're now going to call you, you know, seronegative Greenberg Syndrome, or whatever -- I keep trying for that. No one will use it. But it does change and we live in a world where we're comfortable with that. But Carlos, I want to ask you to comment on even though these things change, the importance of being accurate and being tested relative to treatments. And if you just touch on the acute versus the long term, and what we've tried to do now for years educating our colleagues acutely, even if you don't have the final answer, the importance of intervention, and then long term, what you think the importance of getting it as right as we can in the moment is.

[00:38:04] **Dr. Carlos A. Pardo:** So, I think that one thing that we have learned in the past several decades with myelitis and myelopathies is we need to get, basically, very deep in not only the cause of the problem but also characterize the problem very well. And I think that you mentioned something like acute versus long-term, and there are a couple of things that are very important to understand is if from the beginning we don't get really a very good and accurate assessment of the problem, we may fail in providing a right treatment.

[00:38:42] And I think that the diagnostic consensus and the diagnosis that many of you may receive, based on those consensus criteria are extremely helpful because, again, if we diagnose NMO, we have plenty of opportunity to treat things acutely.

[00:39:02] However, there are many situations in which we don't have the tools. We don't have the antibody. We don't have even the MRI. There are, many of you are very lucky to be in areas of the United States where MRI can be done in one day or two days. There are a lot of people even in the United States in the middle of nowhere where they don't get access to MRIs. So, we need to think about actually to be flexible, and as a clinician, we need to train our people to be efficient in diagnosing neurological problems, neuroimmunological problems, myelitis, and separate the spectrum of myelitis.

[00:39:36] I will take the opportunity here to mention one thing that we are struggling with is the misdiagnosis of transverse myelitis. There is a small percentage of patient that are misdiagnosed with transverse myelitis. And we have taken a look of that after seeing dozen of patient with transverse myelitis. We realized that there are 20% and 30% of people that are misdiagnosed with transverse myelitis. They don't have myelitis. They have spondylotic disease because the cervical spine is present in the spinal cord, and that produce inflammation in the spinal cord. And sometimes that is misdiagnosed as myelitis. And sometimes, there is mistreatment. Patients go and get aggressive treatment. And there is another subgroup of patient that actually don't have either one; myelitis or compression. They have strokes of the spinal cord. And we are trying to refine those

concepts because if we put a patient with a stroke of the spinal cord in plasma exchange, that's malpractice. In other words, it's a difficult situation.

[00:40:38] So, what we need to do in the next several months and years is try to get a more refined approach to the diagnosis. And, again, we know this, we know the recipe. You know what the recipe is? Talk with your patient. Characterize very well what is going on, and grab the test that you are able to get as much as possible, MRI, blood testing. But there is one thing that is very important is we need to be very precise at that moment to generate a very acute treatment. Don't forget that that first stage of treatment is going to end. You are going to continue the rest of the journey with a very important part for the future is the long-term management. And when we have long term management of myelitis and myelopathies, we need to think about a team of people.

[00:41:35] And I always, I am extremely lucky because in Baltimore, I have a fantastic team that is the people at the Kennedy Krieger. And every time that we see a patient with acute disorder or every time that we see a patient come to our clinic, we need to say, ok, we are going to treat you acutely or we treat you acutely, but next is, alright, Christina. We need our patient in your clinic. Okay, Pines, we need our patients in clinic. So in other words, the long-term rehabilitation is also critical. Don't fix too much the money in plasma exchange, IV methylprednisolone. That is important in acute phase. But the aftermath is what our colleagues in physical therapy, occupational therapy are going to be doing.

[00:42:20] **Dr. Benjamin Greenberg:** Yes. We refer to that as the real work. We're just doing the little things. So, we're in the final minute, and I want to give Tammy, and Leslie, and Mike a last word here. If you could each just comment, from an advice perspective, we have a lot of people online, a lot of people in the room. Some people are fortunate enough to live near a center where one of you work or near a center where there's an expert. But for a large part of our population, they live in areas where they may not have the same access to centers of excellence and those types of groups. If people are struggling with, or questioning their diagnosis after this discussion, do you have advice for them on how to talk to their practitioners or how to pursue getting evaluations to ensure their diagnosis is what they think it is or what they've been told? How would you talk to them about it? Besides everybody just go see Mike.

[00:43:16] **Dr. Leslie Benson:** Sounds like a good plan.

[00:43:17] **Dr. Benjamin Greenberg:** His cell phone number is listed online, at the bottom.

[00:43:25] **Dr. Tammy Smith:** I mean, yes, it's challenging. Right? So, I grew up somewhere fairly rural, and, every time my family needs health care, I'm surprised by how challenging it is to get access to excellent health care in rural parts of even the United States much less, other countries. So, I think my advice is just really to do your homework as best you can and then build your team of advocates who can help advocate with you, for you. So, don't just let the interaction between be just between you and your health care provider that you initially see, but bring family and friends with you to those appointments. Look up what is being done in your electronic medical record if you're fortunate enough to be seen somewhere that has an electronic medical record. And then, yes, do your homework about that, and don't be afraid to ask for a second opinion or referral to an academic center. I think physicians practicing in rural places are thrilled that their patients, if they are seeking for second opinions, to get them their referrals they need to get the right answers instead of just having them practice outside their scope of practice or outside their depth.

[00:44:37] **Dr. Leslie Benson:** And I would add that any physician who doesn't support a second, you know, a second opinion is questionable. Like, I'm at a referral center and still I welcome if a patient wants another opinion, I help them find another opinion. I think we also live in a day and an age where hopefully healthcare

is getting a little bit more accessible. So, patients can apply, go through the Internet, and request an online second opinion where an expert can review records and send a letter back to that information for the patient and the provider. And I think seeking out those sorts of resources is good. We've also been able to expand our reach with virtual visits. Right? So you still need an in-person encounter, but some of the follow-up, we can reach for a bit longer with the virtual care post-pandemic. So, I think there are improvements in what we can do for patients who are in more remote areas.

[00:45:32] **Dr. Benjamin Greenberg:** Michael, last one?

[00:45:33] **Dr. Michael Levy:** I would just end by saying that I get this question a lot. I'm in the middle of nowhere. My doctors never heard of this disease, transverse myelitis, whatever. What do I do? And so you don't, your doctor doesn't need to be an expert in this disease. They just have to care. They have to care enough to reach out to an expert, email, phone, whatever, Zoom, and just have a conversation. It only takes us 10, 15, 20 minutes to help advise on the phone, and I think that that's a big difference that we can make.

[00:46:02] **Dr. Benjamin Greenberg:** All right. With that, I wanna actually give a round of applause for both panels, our patient panel and our clinician panel. Thank you for your time.