The Future of Diagnosing Transverse Myelitis

You can watch the video of this podcast at: youtu.be/FGSPYh3ffXA

[00:00:00] **Dr. GG deFiebre:** Hello everyone and welcome. Our 2022 Ask the Expert podcast series is sponsored in part by Alexion, AstraZeneca Rare Disease, Genentech, and Horizon Therapeutics.

[00:00:11] Alexion, AstraZeneca Rare Disease, is a global biopharmaceutical company focused on serving patients with severe and rare disorders through the innovation, development, and commercialization of life-transforming therapeutic products. Their goal is to deliver medical breakthroughs where none currently exist, and they're committed to ensuring that patient perspective and community engagement is always at the forefront of their work.

[00:00:33] Founded more than 40 years ago, Genentech is a leading biotechnology company that discovers, develops, manufactures, and commercializes medicines to treat patients with serious and life-threatening medical conditions. The company, a member of the Roche Group, has headquarters in South San Francisco, California. For additional information about the company, please visit gene.com.

[00:00:53] Horizon is focused on the discovery, development and commercialization of medicines that address critical needs for people impacted by rare, autoimmune, and severe inflammatory diseases. They apply scientific expertise and courage to bring clinically meaningful therapies to patients. Horizon believes science and compassion must work together to transform lives.

[00:01:13] This podcast is entitled "The Future of Diagnosing Transverse Myelitis." My name is GG deFiebre and I will be moderating this podcast. SRNA is a nonprofit that's focused on support, education, and research of rare neuroimmune disorders, and you can learn more about us on our web site at wearesrna.org. For today's podcast, we are pleased to be joined by Dr. Blackburn, Clardy, Flanagan, Greenberg, Levy, and Pardo.

[00:01:41] Dr. Blackburn is a former James T. Lubin Fellow and assistant professor in the Department of Neurology at UT Southwestern Medical Center.

[00:01:48] Dr. Clardy is an associate professor and neurologist in the Division of Neuroimmunology within the Department of Neurology at the University of Utah.

[00:01:56] Dr. Flanagan is a Professor of Neurology and Consultant in the departments of Neurology and Laboratory Medicine and Pathology at the Mayo Clinic.

[00:02:04] Dr. Greenberg, who should be joining us soon, is a neurologist and the Director of the Neurosciences Clinical Research Center at the University of Texas Southwestern Medical Center.

[00:02:12] Dr. Levy is Associate Professor of Neurology at Massachusetts General Hospital and Research Director of the Division of Neuroimmunology and Neuroinfectious Disease.

[00:02:21] And Dr. Pardo is a Professor of Neurology and Pathology at Johns Hopkins University School of Medicine.

[00:02:27] So, welcome and thank you all for joining us today. I'm very excited about this discussion, talking a bit about the history of diagnosing transverse myelitis, what we've learned since then, and where we're going in terms of diagnosing transverse myelitis and what that means.

[00:02:46] So to start, Dr. Pardo, do you mind just talking about the history of what we know as transverse myelitis? When was it first described? And then how was, I know it was the transverse myelitis center at Hopkins at one point now the name is the myelitis and myelopathy center. How was that started at Hopkins?

[00:03:06] **Dr. Carlos Pardo-Villamizar:** Thanks so much GG for the invitation to the podcast and thank you for our colleagues around the country for joining the meeting. Transverse myelitis actually is quite fascinating, interesting term and historically it has been used particularly in the 20th century after the late 40s, and the term transverse myelitis was coined in a paper that was published in 1948 in Lancet, described the presence of myelopathic syndrome that emerged abruptly in a patient with a pneumonia.

[00:03:46] And the terminology has been used on and off or was used on and off in the 50s, 60s, but later after the 70s actually, the term became basically the magic diagnosis for anybody with spinal cord disorders, and most of the literature if everybody has interest in going back to take a look of transverse myelitis actually many papers emerged in the 70s, 80s, and after that a lot of papers in the 90s using the terminology transverse myelitis.

[00:04:20] I believe that our colleagues in the past century actually coined the term transverse because many of the patients that had infectious disorders that evolved to experience myelopathic syndromes actually had a very dramatic enforming and a spinal cord disorder that involved dysfunction in the motor sensory pathways and autonomic dysfunction.

[00:04:48] And it was very equivalent in many ways to what it was observed in patients with spinal cord injury, a traumatic injury. But interestingly at the end of the 19th century, the British neurologist actually already had coined the term infectious myelitis. Early in the century with the upsurge of many viruses that happened in the first part of the 20th century actually, many clinicians coined terminology infectious myelitis, and even at Hopkins, back during the first part of the 20th century, one of our former pioneers of the pediatric neurology, Frankfurt described beautifully in his books, all of the cases of infectious associated myelopathy associated with measles and other type of viral disorders of the period.

[00:05:43] So it is mostly a terminology that was linked in some way to infection and viral infections. And it's very interesting because even now in our clinical practice, every time that we cross with patients with "transverse myelitis" actually, the first thing that we think about is viruses. But interestingly, as many of you have done actually myelopathies are no longer transverse myelitis. It's basically a spectrum of very diverse pathologies including autoimmune associated inflammatory myelopathies or other type of viral associated myelopathies that produce devastating spinal cord disease.

[00:06:27] Back at the end of the 20th century, in 1999, when we established the first transverse myelitis center around the country actually, we used the term transverse myelitis because that is exactly what we learned in our residency training that there were patients with transverse myelitis. But very soon after we start

basically our experience in our center, we discovered that there was a wide spectrum of disorders that were associated with inflammatory myelopathies, acute inflammatory myelopathies. And the major revolution of the myelopathy world happened in the first five years of the 21st century, when our colleagues at the Mayo Clinic described aquaporin-4 as being an antibody that triggered a myelopathic syndrome.

[00:07:14] And this was basically what has been the revolution understanding myelopathies. And as we know right now the diversity in ecological factors contributing to an inflammatory myelopathies is quite broad, and that is one of the reasons we decided two years ago. And said we need to stop; we need to basically stop using the term transverse myelitis and we are encouraging all our colleagues' residents to stop using the term transverse myelitis. And several years ago when Maureen Millie was working with us actually, she presented for the first time a very extensive characteristic of patients, over 500 patients in the American Academy of Neurology, in which she described that many of our patients with transverse myelitis actually were patients with a very diverse group of disorders, including patients that had being diagnosed with transverse myelitis and really had other pathologies like vascular pathologies like strokes of the spinal cord.

[00:08:19] Up to the present, what we know is that actually the term transverse myelitis, we put together what we have seen in our experience over almost 1,200 patients actually 35% of the patients that are labeled transverse myelitis do not have transverse myelitis or myelitis. They have another type of this sort of like a stroke of the spinal cord or dural AV fistula, other things like that. And I think that that observation is similar to what our colleagues in Utah like Stacy Young in the Mayo Clinic has published already in which they see quite diversity of etiological factors contributing to the terminology transverse myelitis.

[00:08:23] So I think that my I'd like to conclude that I have been saying in the past several years, we need to get rid of this term because we are mistreating patients. Patients are getting treatment that they don't need to have when we give the diagnosis transverse myelitis, and we need to encourage our colleagues in the neurology community to modify the diagnosis and focus mostly in an etiological diagnosis rather than using the term transverse myelitis. So, I would stop here. I'd love to hear from my colleagues about the topic.

[00:09:34] **Dr. GG deFiebre:** Yeah. I don't know if anyone else wants to comment kind of on that any of the history or kind of the terminology being used at this time.

[00:09:48] **Dr. Eoin P. Flanagan:** I agree completely. I think the term transverse suggests that it's all the way across the cord, but we have inflammatory myopathy that can involve just a part of the cord. So, I think it causes confusion for people and Dr. Pardo's group has collected so many cases and shown the diversity, that using a different term will help people get to the right diagnosis. So, I think it's bad if you start off with a term that doesn't fit very well then it can lead down the wrong track.

[00:10:23] **Dr. GG deFiebre:** And I guess to follow up, Dr. Flanagan, how has this kind of diagnostic process changed since the discoveries of the antibodies MOG and aquaporin-4 in terms of kind of differentiating different types of myelopathies?

[00:10:39] **Dr. Eoin P. Flanagan:** Yeah, I think it's been a great success story really. The two antibodies discovered that really can give a name to the condition for these patients who previously were told they had idiopathic, or we don't know the cause, cryptogenic, we don't know maybe it was a virus, maybe it was something else. And now we can tell them the exact disease they have and what we need to do about it. And now, in the case of aquaporin-4 antibodies, if you make the diagnosis, we will often recommend that we will generally in all patients recommend long term treatment. So, this can prevent them from having further disability. And these patients used to really have severe issues and we now have three FDA approved medications for these patients. So, this can be life saving for patients. And for the MOG antibody, it's a little bit different and

that some patients will still only have one episode or other patients will go on to have recurrent episodes, but at least we can tell them what to look out for, lots of those patients go on to develop optic neuritis. The other thing to mention is we looked before just to see what proportion and we found about 10-20% of cases of transverse myelitis, when we went back and tested them that were labeled as idiopathic, we were able to discover. So, it accounts for a reasonable proportion of these cases and very important for patient care.

[00:12:01] **Dr. GG deFiebre:** Great thank you. And so, Dr. Levy, I know you've also conducted some research kind of into potential genetic causes of transverse myelitis. How does this research kind of change our understanding or helped our understanding of this diagnosis?

[00:12:17] **Dr. Michael Levy:** Well, we had the opportunity to evaluate two sisters who both had an idiopathic transverse myelitis. And we took advantage of a collaboration between Baylor College of Medicine Johns Hopkins to sequence all the genes in these two sisters, as well as three healthy siblings. And we found a genetic mutation in the two sisters that we didn't think would really be involved in an inflammatory condition like transverse myelitis, but as it turns out these genes might be involved in how proteins are packaged for the immune system to recognize them within the spinal cord. And so, we're looking into this, we have a great fellow coming in next year to start this summer going to look into how these proteins are involved in transverse myelitis, when we didn't really suspect it at all.

[00:13:18] And that just goes to show you that even though genetic causes of transverse myelitis might make up a very small minority. I think we found a total of eight out of hundreds that we've surveyed, it just goes to show you that we can still learn a lot about these few patients and maybe extrapolate that and try to understand how the disease occurs at all. And maybe those processes are also involved in patients who don't have genetic causes of transverse myelitis. So, stay tuned for updates on this research next year.

[00:13:54] **Dr. GG deFiebre:** Great, thank you. And Dr. Clardy I know you recently also published a study looking at transverse myelitis in the VA Health System. And so, I was wondering if you could comment on how this paper and the findings kind of maybe change our understanding of how common this diagnosis is or what this paper kind of contributed to the understanding of this diagnosis?

[00:14:17] **Dr. Stacey Clardy:** Yeah, it's a great question. And thanks to the foundation for supporting this. Two of our fellows actually worked on this project a great deal, we set out to do this and perhaps underestimated the number of veterans in the whole entire national system that would have this diagnosis, or rather it was considered for them. So, we sifted really through close to 5,000 charts by hand. Kudos to Michael Sweeney and Jonathan Galli. I don't think we quite knew what we're getting into ahead of time, but so glad that we did it. And I think we confirmed a lot of what we've already talked about today. And Hopkins and Mayo had previously put out some research about what myelopathy looked like, when it came to a quaternary referral center.

[00:15:11] And in a way, what we were doing was sort of in reverse verifying what they found, much of what they found in those papers, and Carlos and Eoin could probably speak to this, was that of the cases that ended up at a quaternary referral center, several had not even had cerebral spinal fluid analysis. And in fact, we found the same thing in looking at this large national cohort. So, it highlighted to me, we have a lot of work to do is the bottom line on the neurology side in educating our colleagues. If we're considering this diagnosis seriously and not even looking at spinal fluid, we're already sort of, kind of making it difficult to get the accurate cause or the accurate diagnosis.

[00:15:56] To get back to your question too, the original reason we wanted to do this was when I was digging around in the literature and went all the way really back to the NIH and NINDS web site looking anywhere for

how common is this condition, I couldn't really find anything, there was a brochure that cited a reference that was about 30 years old and I couldn't really tell how accurate that might be. So, we really did want to get a feel for that, and it's perhaps more common I think than we thought at least based on the literature. I don't think anybody on this phone call was surprised, but we found about eight cases per 100,000 by prevalence.

[00:16:33] We hesitated to go more into sort of incidents because it gets a bit complicated, especially with the large time period over which we were following, we followed these veterans in the study, they were seen at the VA an average of 12 years. So, it was really, I think a good look, but definitely highlighted to me that we've got a lot of work left to do. Many of them also didn't have what I think many on this this call would consider an accurate treatment trial either and they had a high level of disability, right. We measure that in many of our retrospective studies by something called the modified ranking score, it's a scale from 0 to 5, but many of them were coming out at around a three.

[00:17:18] And I think we would all agree we would hope we could do much better than that in the modern era, but again, this was a longitudinal study and so really just sort of put some numbers to the sense and the hunch that we all had, and really laid down, I think the sort of the framework for where we need to go to improve.

[00:17:40] **Dr. GG deFiebre:** Great, thank you. And Dr. Greenberg, there were criteria that were published up for TM in 2002. How has our diagnostic process kind of changed in the past 20 years, I can't believe 2002 was 20 years ago, but?

[00:17:55] **Dr. Benjamin Greenberg:** I'm having a hard time believing that as well. And so, a lot has changed, I mean, when we think about the fact that in 2002, we didn't have the anti-aquaporin-4 antibody test. We didn't have the anti-MOG antibody test. There was a complete lack of systematic analysis, looking for vascular lesions of the spinal cord, and a lack of awareness around certain patterns for neurosarcoidosis presenting with myelopathy. I mean it's really eons ago, from a discovery perspective. And so, with the recognition of all of these causes of myelopathy and myelitis, we've been able to differentiate among our patients who used to carry the name transverse myelitis as a diagnosis and really work them down into subgroups.

[00:18:54] One of the things that's interesting for example, if you look at the anti-MOG antibody associated disorder, individuals with those illnesses can have relapses separated by years or more than a decade if they're having relapses. And so, in a paper talking about idiopathic transverse myelitis, we would be thrilled to talk about five year follow up in cohorts. Well, that's nothing when we're talking about an anti-MOG associated disorder. And so, people who we had labeled as idiopathic may have subsequently gone on to have a relapse, and we wouldn't have known it. And so, as we chip away at the molecular biology and the work Mike's done on genetics and looking for atypical myelopathies.

[00:19:36] The world of idiopathic transverse myelitis is getting smaller and smaller, which is a good thing. I used to joke in lectures, some people have heard me say idiopathic means the doctor is an idiot and pathetic for not being able to find the cause idiopathic. And as we're getting better at what we do, the number of people left without an answer as to why is getting smaller. And so, it's really changed our approach to diagnosis, we are looking to do angiography in more patients than we used to. We're looking to send a broader systemic work up for autoimmune disease than we used to. And we're being cautious with the labels that we provide to folks.

[00:20:16] Kyle Blackburn had led a paper talking about dropping the word transverse from the name, that it's probably time we redid the nomenclature and really just talked about myelitis. And because the notion of transverse myelitis being a standalone diagnosis has confused many people for many years, and I think we're

getting to a place now where we can finally clean up the language, so we do a better job of communicating to our patients what they have and hopefully why they have it.

[00:20:49] **Dr. GG deFiebre:** Great, thank you. And then Dr. Pardo I know you talked a little bit about kind of potential vascular causes of myelopathies, I know that you published a paper I guess a couple of years ago at this point now, but how did this, what you found in terms of the vascular causes of myelopathies, how does that kind of change our perspective on diagnosing transverse myelitis work, other forms of myelopathy?

[00:21:15] **Dr. Carlos Pardo-Villamizar:** So, the observations that we have on vascular myelopathies, both acute and chronic are based on the observation that many patients referred to our center with the diagnosis of transverse myelitis end up having either strokes of the spinal cord or chronic evolving vascular lesions associated with your dural AV fistulas. And they have a couple of publications, particularly on the chronic evolving pathology and we have made some other papers for analyzing what is going on with those patients that are diagnosed by, misdiagnosis with strokes and treated as transverse myelitis.

[00:22:01] The bottom line is that overall based on what we have seen, and I believe Dr. Flanagan has stated in other publications, similar observation is that approximately between 10% and 20% of patients with the diagnosis transverse myelitis actually they have vascular myelopathies. And the main message is it's extremely important that our colleagues in the community identify those patients because unfortunately what we have observed is that many of those patients during the acute phase actually undergo treatments as in "transverse myelitis" and they go on IV methylprednisolone, plasma exchange, even aggressive treatment with immunosuppressive medication when they have just obstructed spinal cord.

[00:22:54] And that is a very difficult situation because actually we are worsening the clinical situation on many of those patients by doing that. So, I think that the emphasis that we are doing now is make sure that the diagnosis during the acute phase is correct and there are several aspects of the clinical assessment that give basically good sources of information. Patients that during the acute phase have normal spinal fluid, this is a flag to say, wait a minute, is this really inflammatory? Is this really myelitis? Is this really associated with an autoimmune inflammatory disorder?

[00:23:35] So there are several aspects of the clinical assessment and the approach in the diagnosis of the patient that is telling us that those patients need to be evaluated carefully and those patients probably don't have inflammatory myelopathy. The same happened with the MRI. The assessment of the MRI magnetic resonance imaging of the spinal cord is becoming a very good tool and we are now identifying several patterns that allow us a better diagnosis of vascular myelopathic syndrome. So, I think that the clinicians in the community need to be educated and need to be aware that strokes happen in the spinal cord, that strokes happen in children, and strokes happen in adults and that the clinical profile is very different to the typical profile of patients with demyelinating myelopathies or autoimmune associated myelopathies.

[00:24:34] So that is what we may need to emphasize and perhaps the work that the group has been doing in the past several years trying to modify the diagnostic criteria is going to be extremely beneficial, we need to get rid of the transverse, as Dr. Greenberg stated, that's a misnomer, and that is misleading the management of many of our patients.

[00:24:56] **Dr. GG deFiebre:** Great. Yeah, so, to transition I guess Dr. Blackburn, I know Dr. Greenberg said that you've worked on the paper about removing that word in the beginning. So, do you mind just talking a bit about that and also maybe how during your time as a resident and then fellow, how the diagnostic process has kind of changed over time you've noticed?

[00:25:17] **Dr. Kyle Blackburn:** Absolutely. So, I guess the first thing is I think is everyone is saying there's a little bit of a movement kind of internally to drop the term transverse from transverse myelitis, and I think there's a case being made now that we have a better understanding of specific ideologies that we can do that and feel more comfortable in doing that. Since I've been a resident, a fellow, there's been really a lot of work done that has been done by a lot of the people in this call actually that has influenced how we approach these cases. So, probably one of the first things that I would emphasize is just how we've started looking at our imaging in more detail and using what we see on imaging to actually guide our thought process early on in the diagnostic process.

[00:26:09] So now in today's world we actually have residents whenever they contact us about a case, they're often giving me ideas about ideology based on what they're seeing on imaging. And I think 15-20 years ago it was really, "Does this look like multiple sclerosis? No, I think this is transverse myelitis." And that's as far as we got and that's a really exciting change. Of course, during my time in training, the MOG-antibody became widely available and certainly that has helped elucidate some cases that would have been labeled as idiopathic. And then I'll also say I came of age during the rise of AFM, in 2014 and 2016. So, I saw all of this new cause of myelopathy, predominantly in children, rise. So, that's how the landscape has changed over the last about six years.

[00:27:01] **Dr. GG deFiebre:** Great, so thank you all. And I'm going to open this up to everyone, whoever wants to respond. So, there's been discussions about changing the terminology we use, using different diagnostic tools and maybe different ways or obviously having new testing like the antibody testing. So, what kind of changes do you foresee to potential diagnostic criteria in the process that someone would undergo to get to this diagnosis?

[00:27:30] **Dr. Benjamin Greenberg:** Yeah. I think we're going to see hopefully several things. I think everybody on this call is committed to and aware of efforts to bring together the community to formally update the diagnostic criteria, and I'd love to see that happen in this year and come out and fill in some of the holes from the old criteria that have just evolved as we have evolved, but also I think one of the critical things is independent of the final buckets that patients get assigned, the final titles, is the work up and the evaluation. And I think as a field, what we really want to see happen is patients getting the appropriate workups at the time of presentation, and not having to travel to specialty centers to fill in gaps.

[00:28:22] I think we have seen the widespread adoption of testing with the anti-aquaporin-4 antibody which I think was a major step forward for the field of neuroimmunology, multiple sclerosis, transverse myelitis, neuromyelitis optica. I think we're seeing a similar spread of testing with the anti-MOG antibody, but what we haven't yet seen, at least I haven't yet seen, is widespread skills at referring patients for angiography appropriately, and then also appropriate angiography is being done. I think we still see a lot of patients for whom there is a high suspicion for a vascular event and perhaps inadequate vascular studies being performed to the spinal cord.

[00:29:06] And unfortunately, that test isn't just a lab test, and is much more complicated to do and is user dependent. And it really speaks to the need for us to engage collaboratively with our colleagues in interventional neuroradiology and get them comfortable with doing more of these exams and doing them in a complete fashion. So, I think there's work to do on the semantics, work to do on the categorizations, but also work to do on raising awareness on how to manage patients in real time.

[00:29:42] **Dr. Carlos Pardo-Villamizar:** So that's a very good point. And I think that one of the important steps in the next several months is to make sure that there is a good implementation, and of a very good

algorithm, an approach to evaluate patients with acute myelopathic syndromes, acute and sub-acute chronic myelopathic syndrome. So, I think that identifying the right diagnosis is identifying the right etiology and we are not able to treat correctly a patient with an acute myelopathy if we don't identify correctly the etiology. Treating NMO is very different to treat a demyelinating myelopathy. Treating NMO is different to treating a patient with MOG.

[00:30:27] So I would like to emphasize that we need to educate the community about what are the different steps as Dr. Greenberg outlined very well. There are very clear steps that are easy to be done. The great thing that we have in the past several years is to have access to the immunological access for diagnosis. One of the major limitations is the lack of access to good imaging of the vascular supply to the spinal cord. I really am staying away now to say that we need to have angiograms for everybody that we are diagnosing with vascular myelopathy, because the reality is number one it is difficult to be performed in every center and number two, there are a lot of technical difficulties.

[00:31:16] And number three, remember the blood supply, the vascular system is very dynamic, so two or three days after the stroke, the blood vessel may be recognized, we are no longer able to see the occlusion or other factors may influence the outcome of that test. So, I think that we need to be very practical, and we need to outline the different aspects of what we are going to do acutely with patients, and how we are going to manage and what is the type of test that we need to acquire for establishing the right diagnosis.

[00:31:48] **Dr. Eoin P. Flanagan:** I can make a quick comment just to say, Dr. Pardo has published extensively on a few things that can be really useful clues that we don't even need a test for, which is the age of the patient, the sex of the patient, and the time from the onset of symptoms to the maximal deficit, and if you use those three you're going to get close to the right answer a lot of the time. So, I think there's a lot of confusion out there where patients have a slow gradual progression and have more of a chronic course and that doesn't fit well with a lot of myelitis. So, I think when the criteria come it will need to stratify the cases from a very sudden onset to kind of an acute, sub-acute, and then a more chronic. And that can really help in distinguishing the different causes.

[00:32:39] **Dr. Michael Levy:** GG, can I make a counter argument against getting rid of transverse? My sense is that most doctors have heard of transverse myelitis, and if we take away that term, I'm afraid that we're going to deprive them of an opportunity to refer patients to us. And while we can go through the algorithm and order angiograms and figure out patterns on MRI that might predict one type of myelitis from another, I'm worried if we get rid of the term transverse myelitis, it's going to disrupt the whole community of referrals that come in. I mean remember even the former name of the Siegel Neuroimmune Disease Association was Transverse Myelitis Association because that's how they come in, and if we want to improve on the semantics, we can expand it. We can call it transverse myelitis spectrum disorder or something like that, but I don't think we necessarily need to get rid of the term externally, we just need to get better at defining it internally. That's my argument.

[00:33:49] **Dr. Benjamin Greenberg:** I'm not as worried as Mike. I think the world can adjust and move forward. We used to call some of these things Landry's paralysis and Hopkins syndrome and now we call it AFM, but the world moves on. I think your point is well taken and I know we get a lot of questions about treatments and management of patients and sometimes discussions around semantics and names can be dry. But I'll just point out that if heterogeneous patients are lumped together, then research around therapies and cures is dramatically hindered, because we'll never understand why one treatment worked for patient A and not patient B if they had the same "diagnosis."

[00:34:39] And so being exact in the words we use to describe patients is mission critical for getting like groups of patients together in order to identify the best therapeutic interventions for those patients, before there were ST elevation myocardial infarction heart attacks and non-ST elevation myocardial infarctions. It didn't make sense why some treatments worked in some and not the other and so categorization is sometimes boring and has risk. And Mike, I think you're right that there is a downside to changing names, but I do think it's important for the field to overall advance so we can get better treatments.

[00:35:25] **Dr. GG deFiebre:** Agreed. And yeah, I mean I think obviously discussing the semantics or the terminology used is important to then get these kind of diagnostic buckets to then be able to have treatments and potentially restorative things for the diagnosis. So, Dr. Clardy were you going to say something, I saw you unmuted?

[00:35:44] **Dr. Stacey Clardy:** No, I think we could go around. I agree they're going to find you, Dr. Levy, especially because most of the referrals come from colleagues, and what I teach my fellows is you have to earn the term transverse myelitis by working first through the differential from myelopathy, right? You have to prove that it's inflammatory, which is what the "itis" at the end there sort of implies. But yeah, I think any time someone sees one of these lesions in the spinal cord amongst our colleagues that is not in this field, I think they find us very quickly to try to, in most cases, to try to help out and sort an answer.

[00:36:24] **Dr. GG deFiebre:** And so, I guess my question as someone who has been diagnosed with idiopathic transverse myelitis, and there are many people that I know who have been, what would this kind of change in terminology or changing this mean? Is the goal to kind of not have that category exist anymore? What does all of this kind of entail for someone's day to day life or how they get treatments or that sort of thing? I'm just curious.

[00:36:57] **Dr. Carlos Pardo-Villamizar:** So, I'm going to jump on answering that question because actually that related with one of the questions in the chat, the issue is, yes, the issue is semantic and categories and that will allow us to predict what is going to happen in the future. We recognize easily now that patients with neuromyelitis optica actually frequently developed but in very difficult intractable pain. And that actually is extremely important because we can identify patients that prospectively we can be more focused in treating potential bad outcomes. And the thing happened with strokes of the spinal cord. If we identify correctly acute vascular myelopathy, we can identify risk factors that led to that vascular myelopathy and trying to modify those risk factors so we can actually help the patients to modify the risk factors and prevent other potential problems.

[00:37:57] And the same in the situation between demyelinating diseases of the spinal cord. Remember when we were diagnosing NMO, we initially treated patients with interferon treatment. Those patients worsened. So, identifying correctly the category, if this is NMO, we know that we need to stay away of interferons. And we have better treatments now that are going to be very beneficial for potential outcomes in the future.

[00:38:29] So, that's the benefit of including a very precise diagnosis at the beginning of the myelopathic syndrome. We are going to end up with the group idiopathic myelopathies as well, idiopathic myelitis. We are going to end up but, as was mentioned by Dr. Greenberg, eventually those patients will turn out to be NMO later or MOG later. But we need to raise a better level of awareness among clinicians to say, okay, you need to be alert to have this diagnosis and establish a better diagnosis and treatment in the future.

[00:39:09] **Dr. GG deFiebre:** Any other comments?

[00:39:15] **Dr. Kyle Blackburn:** I will say, I always think there's going to be a role for an idiopathic category, at least in the very near future in these disorders. I think everyone here has seen a patient that despite all the testing, that the etiology still remains unclear, and it may be that something happened that would have been acutely apparent, had we done a certain test at that moment, when it was going on, but that time has passed. Now they're seeing us a few years down the road. So, I still think there will be a label of some sort for idiopathic or crypto generic, whatever your preferred term is, it just may be, it'll certainly be a smaller proportion of patients with a new group of criteria that meet that definition. And I think it may be worded differently than it is in the current criteria.

[00:40:07] **Dr. Eoin P. Flanagan:** I think it's important to remember, I know there's some mention about cure in the chat but sometimes the best cure is immediately in guiding our treatment. If a patient has an aquaporin-4 antibody positivity for example, and a myelitis, we're really going to be using plasma exchange in the vast majority of those patients. So, it can really be important and that can be where we can really prevent the disability. So, it can be really crucial in terms of patient outcomes.

[00:40:46] **Dr. GG deFiebre:** So, we've talked a bit about the idiopathic transverse myelitis or disease associated myelitis. So, what are these terms mean, and what about vascular versus inflammatory? How do we differentiate between these two during the diagnostic process?

[00:41:08] **Dr. Benjamin Greenberg:** Yeah, I think in terms of the second part, first, in terms of identifying vascular, it's first having a level of suspicion based on the history. Despite all of our technologies, all of our blood-based tests, it's still important for a health care provider to take a careful history from patients, and to look for any of the red flags that would lead somebody to be concerned about a vascular event of the spinal cord, and it's important to recognize there are lots of different types of vascular events of the spinal cord. So, sometimes an artery that feeds the cord can be blocked, leading to a lack of blood flow. Sometimes it's a vein that's draining the spinal cord that's blocked. And sometimes people have an abnormal connection between arteries and veins called a fistula. That can lead to funny pressures in the cord.

[00:41:57] And each of these can present slightly differently. Some of them can present with a rapid evolution of symptoms with, where somebody goes from perfectly normal to profoundly disabled in under six hours. And whenever we hear that history, I think everybody on the call would agree that should be a red flag to look for blood flow issues related to the cord. Likewise, when we hear about recurrent events as particularly in older populations with back pain and when the MRI doesn't exactly fit for a classic inflammatory lesion, we should look for these dural AV fistulas. A lot of these are missed and people are told they have recurrent myelitis when in fact they have an intrinsic problem with blood flow to the cord.

[00:42:44] And then this is the really frustrating part. Once you have a suspicion that there's a blood flow problem to the cord, you have to work with an appropriately skilled neuro-interventional radiologist to do the diagnostic studies, an angiogram, in order to see if there's an abnormality. And so, I think we have a long way to go to raising awareness about what some of the red flags of these conditions are. Carlos has done a lot of work over the last several years. Looking back at the history of patients who have gone to the Johns Hopkins transverse myelitis center, where in retrospect, on careful review of their charts, while they may have come in with the diagnosis of transverse myelitis, the most likely etiology was vascular. And I think it's fair to say, Carlos, that a lot of those decisions are based on the history that the patient told you, and sometimes or often supported by some atypical MRI findings, but that first step is really how the patient tells their story.

[00:43:49] **Dr. Carlos Pardo-Villamizar:** That's correct. And actually, that is one of the emphases that we are giving to our residents and fellows now, is talking with the patients and listening to the patient very carefully at the evolution of the symptoms. Establishing the temporal profile of the symptoms and the characteristic

of the symptoms are very key for the diagnosis and the right diagnosis, but I'd like to move a little bit on the future. And actually, we encounter all of these patients that get tons of exams, tons of blood testing, including NMO, MOG, and other antibodies and we find nothing. And I really think that what Michael, Dr. Levy, is doing with the generic part of the myelopathic syndrome is very important and it's going to be very important for the future.

[00:44:38] Particularly because as we are seeing now in demyelinating disorders of the brain and in many other neuroimmunological disorders, this is a group, a subset of those patients that actually we are able now to identify better to have polymorphism in the genes, gene modifications that lead to very rare variations of immunological responses that are given demyelinating disease, white matter disorders. And we need to have a much better way to explore our patients with idiopathic myelitis because I guarantee that some of those patients actually fit in the group of patients in which there are genetic variations that are influencing the development of these myelopathic syndromes.

[00:45:24] So I think that we need to pay attention to that in the future and dedicate more effort to understand the host and to understand what the genetic susceptibility that patients may have for developing spinal cord disorders that are not necessarily exclusively inflammatory. It may be actually metabolic disturbances that damaged the myelin, another sort of abnormalities that eventually will give us a better explanation for those idiopathic myelopathies.

[00:45:55] **Dr. GG deFiebre:** Have anything else to add, I guess, Dr. Clardy, I don't know if you had any comments about the vascular, I saw you unmute at one point.

[00:46:11] **Dr. Stacey Clardy:** Very observant. I was just going to say I think it was maybe, was it Carlos's paper, I'm not sure which one right, but I think the most powerful thing that's easy for sort of the non-neuroimmunologists to remember is the time. And it is. You can get that in a five-minute history, "When did you have your first onset of symptoms? And at what point did it drop to the worst level? When were you the most severe?" I just did that this week in clinic actually. Bennett was a patient I think you had sent over our way. And sure enough, the answer was 12 hours. And so that patient is going for his final angio this week because it's just right there, that was it, question done. We sort of had the plan after the answer to that question in terms of hinting at a really vascular cause.

[00:47:01] **Dr. Eoin P. Flanagan:** The other thing to mention, just about some of the fistulas are treatable. So, it's really, really important not to miss the dural arteriovenous fistula because the problem is once the damage is done in the spinal cord, it's quite difficult to reverse it for some of these conditions. So, the earlier we can detect it, the better, and we've all seen patients where it's taken too long and then they struggle, so it's really disappointing to see that. So, I think we have to remember particularly that one, that we can fix quite readily with our neurosurgeons or with certain radiology techniques.

[00:47:42] **Dr. Carlos Pardo-Villamizar:** I think that in the chat there is a very interesting question. For patients that have been diagnosed many years ago, like 20 years ago, if it's worth it to go back and reanalyze the situation and change diagnosis? So, it will be interesting to give an opinion about that too. So, to clarify that question?

[00:48:08] **Dr. Michael Levy:** that raises in my mind the question about cures and long-term outcomes, and people who have attacks years ago and are at this point now and they're wondering, "What does my future look like? What kind of cures are you working on? What kind of remyelination or recovery regeneration therapy are you working on?" I wonder if this audience, if this panel thinks that it matters which diagnosis you have in terms of what you will respond to or if spinal cord injury five years after an attack, whether it's vascular

or NMO or whatever. If it was a damage done, can all of those people potentially benefit from some sort of restorative or remyelination therapy?

[00:49:03] **Dr. Stacey Clardy:** Are you leading the witness there, Dr. Levy?

[00:49:06] **Dr. Michael Levy:** I'm just curious, is this the type of recovery therapy that we're going to have to put into bins? Restorative therapy for NMO, recovery therapy, MOG patients recover well on their own, they may not need any, but idiopathic TM, vascular. Is each category going to have its own stem cell trial or do they share some common pathology that maybe they can all respond to? What does everyone think the future looks like for these people? I see the questions in the chat about cures and recovery? I'm just curious what you think.

[00:49:41] **Dr. Benjamin Greenberg:** Michael, I think it's a great question and I think the answer is in the end there will be therapies that definitely cross over regardless of the cause. The goal with the restorative therapies we're working on is whether your spinal cord was damaged by idiopathic transverse myelitis or anti-MOG associated transverse myelitis to have a therapy to help both. But the clinical trials to get those therapies approved will have to be done in homogeneous patient populations. I'll give you an example. Our current stem cell trial for transverse myelitis, and we hope to have our first patient in the operating room in in March or April, excludes individuals with the anti-aquaporin-4 antibody and the reason for this is a technical one.

[00:50:33] One of the concerns we have when we put stem cells into the spinal cord is they could elicit an immune response and cause new myelitis like rejecting an organ in an organ transplant. So, our patients are going to be immunosuppressed to prevent that event. But in the course of a trial if we enrolled a person with the anti-aquaoporin-4 antibody and during the course of follow up they had a new myelitis, it would be very difficult to tell the difference between an NMO relapse versus a response to the transplanted cells. So, from a clinical trial design perspective, I think the trials will be done in individual patient populations to control for some of these issues. But once we have therapies that work, I think we would apply them across the spectrum of spinal cord patients.

[00:51:23] **Dr. Eoin P. Flanagan:** I think there's a question in the chat about the COVID vaccine, and maybe it's topical to cover that. In general, I think even for patients who had myelitis triggered by a different vaccine, the COVID vaccine is quite different, and I think we've been recommending it in all our patients. We've actually seen a lot more problems with patients developing inflammation secondary to the infection than, versus secondary to the vaccine. So, I think, we strongly recommend the COVID vaccine and try to have all our patients boosted, particularly those on immunosuppressants where that might put them at a bit of higher risk.

[00:52:05] **Dr. GG deFiebre:** Great, thank you for responding to that. So, we just have a few minutes left. I was hoping you could all kind of give some final thoughts and as SRNA, we plan to continue this conversation, and engage more with the broader medical community as well to improve the diagnosis of myelitis and myelopathy, which, well as we've talked about, impact treatments and prognosis and potentially a cure in the future. So, I guess I'd just like to open it up and see if anyone has any final thoughts to share.

[00:52:42] **Dr. Eoin P. Flanagan:** I can give a quick final thought. I'll just say, I think the future looks good. We've made a lot of advances over the last 20 years, and I think a lot of those advances have been based on patients giving research samples and helping us discover these things, and we really appreciate all the things that patients have given us that have allowed us to learn about these diseases and how to treat them. So, it's really a thank you and I think we're making good progress. And we're all here together and we want

to work together to kind of fix this. So, I think there's a real effort out there to try and focus on myelitis and treatments and helping patients.

[00:53:21] **Dr. Carlos Pardo-Villamizar:** I agree 100% with those statements, and it's extremely important that patients and families keep the focus on the future. And again, there are a lot of frustrations, and every week we experience that frustration. The frustration that you have with chronic pain, or chronic weakness, or spasticity, it's the same frustration that we have not being able to treat correctly or improving that situation. So, I think that in the near future we need to pay more attention to improve the quality of life, particularly pain, I think pain is a nightmare, we have a lot of medication for pain. We have been successfully treating patients for that pain and I think that the effort from many institutions, NIH and other institutions are funding research should focus on helping us to get better treatment for pain management, in patients with myelitis and myelopathies in general.

[00:54:28] **Dr. Stacey Clardy:** Yeah, I think advocacy is a big thing and advocating for yourself. Obviously, you have some people in this call who are quite passionate about trying to move the needle forward in this condition, but with the Internet now, I think, coming prepared to ask the hard questions to your docs, I think we like that. I think we value that every time I can tell that a patient has put some thought into things, it really helps to make a difference. So, because sometimes we do just get caught all up in symptom management, and so if that's not what's on your mind, and if your mind is let's look more for why did this happen or let's look more for rehabilitation and creative avenues there, I think really just saying your top priorities every time for the visit and advocating that way, really helps to move things forward to get the most out of what's currently available we have to offer.

[00:55:30] Even saying I have some patients that say I want to be first on the list, the second trial comes for X. Alright, we remember that. So really, don't underestimate the impact you have on your physician when you come in with a pointed list of goals and keep doing that because it is the patients that are moving this forward.

[00:55:51] **Dr. Benjamin Greenberg:** Yeah. And if I can just shortly dovetail on Stacy's comment about advocacy. Self-advocacy is so important and then community wide advocacy also important and the SRNA through programs like this I think does a wonderful job of keeping community connected, but I do want to put out a plea to everyone listening as you get those emails from the SRNA with surveys or registries, and it takes so much time to get your records together and put in data. It is time that is well spent. The information that's gathered by those types of survey studies where we're asking you the community questions is really important because we, all the different specialists on this call only get one small sliver of a view of the community based on whoever comes to our clinic.

[00:56:39] And it is so important for us to understand the community at large, as a whole internationally and so if I had to put a plea out there it would be to take the time when you can to answer those surveys because the data is actually very meaningful.

[00:56:56] **Dr. GG deFiebre:** Thank you. And then, Dr. Blackburn.

[00:57:02] **Dr. Kyle Blackburn:** Sure. So, I think the whole, to kind of wrap everything up, the whole discussion today is around changing how we think about these things by defining potentially a new nomenclature and I do think that's really important. I think that that's going to lead people in the very early phases of the disease to identify the right diagnosis earlier, apply the appropriate treatment to minimize damage in the acute phase, which is critical, identify people that are at high risk of relapse to prevent that from happening. And

then of course we focus on by identifying these things and more and more fine-tooth ways, the ways to help recovery. So, I think this is just the first step in a long succession of work to come.

[00:57:57] **Dr. GG deFiebre:** Great. And Dr. Levy?

[00:58:03] **Dr. Michael Levy:** I'm excited about the opportunity to do research in this area. And I think that we're going to continue to carve up the classification of transverse myelitis into smaller groups of homogeneous patient groups and then we'll be able to do good research on treatment for all of them. So, stay tuned.

[00:58:27] **Dr. GG deFiebre:** Great. Well, thank you all so much for chatting with me and also responding to the comments. I really appreciate that as well. You are wonderful. So, thank you so much and we look forward to continuing this conversation. And yeah, thank you. Have a great weekend, everyone.

[00:58:44] **Dr. Carlos Pardo-Villamizar:** Thank you Dr. Gabrielle.

[00:58:46] **Dr. Eoin P. Flanagan:** Thank you.

[00:58:48] **Dr. Stacey Clardy:** Thank you.

[00:58:49] **Dr. Benjamin Greenberg:** Thank you.