

The Transverse Myelitis Association 'Ask the Expert' Podcast Series
2018 Podcast on Acute Flaccid Myelitis

The audio of this podcast is available at

- GG deFiebre: 00:00:01 Hello everyone and welcome to the TMA Ask the Expert podcast series. This one is entitled 2018 Podcast on Acute Flaccid Myelitis. My name is Gg deFiebre and I will be moderating this podcast. The TMA is a nonprofit focused on support, education and research of rare neuro-immune disorders. You can learn more about us on our website at myelitis.org. This podcast is being recorded and will be made available on the TMA website and for download via iTunes. During the call, if you have any additional questions, you can send a message through the chat option available with Goto Webinar. For today's podcast, we are pleased to be joined by Dr. Benjamin Greenberg and Dr. Carlos Pardo. Dr. Greenberg received his Bachelor of Arts degree from Johns Hopkins University and his Master's Degree in Molecular Microbiology and Immunology from the Johns Hopkins School of Public Health in Baltimore, Maryland. He completed his residency in neurology at The Johns Hopkins Hospital and then joined the faculty within the division of neuroimmunology. In January of 2009,
- GG deFiebre: 00:01:04 he was recruited to the faculty at the University of Texas Southwestern Medical Center where he was named Deputy Director of the Multiple Sclerosis program and Director of the new Transverse Myelitis and Neuromyelitis Optica Program. Dr. Greenberg is recognized internationally as an expert in rare autoimmune disorders of the central nervous system. His research interests are in both the diagnosis and treatment of transverse myelitis, neuromyelitis optica, encephalitis, multiple sclerosis, and infections of the central nervous system. His current, he currently serves as the Director of the Neurosciences Clinical Research Center, and is a Cain Denius Foundation Scholar. Dr. Carlos. Pardo is an Associate Professor of Neurology in the Division of Neuroimmunology and Neuroinfectious Disorders and Pathology at Johns Hopkins University School of Medicine in Baltimore, Maryland. He is the principal investigator of the Neuroimmunopathology Laboratory, member of the HIV Neurosciences Research Group and clinical neurologist at the Multiple Sclerosis and Transverse Myelitis Centers at Johns Hopkins Hospital. His clinical specialization is on neuroimmunological and infectious disorders of the nervous system, with particular focus on multiple sclerosis, transverse myelitis, neurosarcoidosis, and neurological complications of autoimmune disorders. So welcome and thank you both for joining us today. We really appreciate it.

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- Dr. Greenberg: 00:02:30 Happy to be here.
- Dr. Pardo: 00:02:32 Thank you for the invitation, GG. Happy to be here too.
- GG: 00:02:35 Thank you. So we wanted to do this podcast because we've been hearing about an increase in cases of acute flaccid myelitis. Um, and so to start I would just like us to talk a little bit about what acute flaccid myelitis is and what the difference between TM, classic TM, and AFM is and how they present differently. Dr. Greenberg?
- Dr. Greenberg: 00:03:03 So the critical portion of acute flaccid myelitis, what separates this out as a subset or variant of transverse myelitis, is the part of the spinal cord that gets the predominant amount of damage. So from a motor control perspective, there are two different wires that are responsible for the transmission of motor impulses from the brain to the muscle. The first wire originates in the brain and descends in the spinal cord where it attaches to a second wire, a second neuron, that goes out to the muscle.
- Dr. Greenberg: 00:03:46 When you damage the beginning of that very second wire, that second neuron, that neuron which lives in a part of the spinal cord called the gray matter, leads to a certain pattern of weakness. It's defined as flaccid weakness, where the limbs are not just weak, but they're loose like spaghetti and people will lose the typical reflexes that we can find on a physical exam. Whereas, when you damage the first wire, the wire that's in the spinal cord on its way down from the brain, the weakness that results has increased tone and increased reflexes. It's a different pattern of weakness depending on which wire gets affected. In each scenario, we think there is some degree of inflammation in the spinal cord, whether the inflammation is there by mistake in the setting of an autoimmune myelitis, or if the inflammation is there to fight an infection, as in the setting of a virally-induced myelitis, we think that the acute flaccid myelitis is just a variant where the predominant damage is occurring in the gray matter affecting that second wire in the system. The reason the differentiation is important is, we think, the causes of acute flaccid myelitis differ than the causes of what we see in white matter transverse myelitis. And, uh, because there's a different presentation and potentially a different ideology, our approach to these two conditions has some overlap, but also some very unique steps that we take.
- GG deFiebre: 00:05:36 Got it. Dr. Pardo, do you have anything to add to that?

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- Dr. Pardo: 00:05:40 So I think that that's an excellent explanation about what is acute flaccid myelitis, but let me go back a little bit to the clinical issues and what is called a flaccid myelitis. The bottom line as Dr. Greenberg explained, is this is an inflammation of the spinal cord. The inflammation of the cord is very selective in the gray matter of the spinal cord as compared with other cases of myelitis. And the term flaccid means that patients are frequently very floppy, so they develop weakness and they are not able to move legs or arms, and those muscle groups are basically without any evidence of muscle tone, and that is the definition of flaccid. But the other thing that is very important to differentiate from other causes of transverse myelitis is, this is an acute and very full minute disorder. In other words, as compared with cases of myelitis associated with some autoimmune disorders like neuromyelitis optica, autoimmune disorders like multiple sclerosis or even some post-infectious problems, acute flaccid myelitis is a very full minute illness that happens in a matter of hours or couple of days. So most of the patients actually develop neurological problems in a short period of time following an upper respiratory infection or following an infectious syndrome. So that is the meaning of the terminology acute flaccid myelitis.
- GG deFiebre: 00:07:19 Great. Thank you. And are there any differences in the presentation other than, you know, just the floppiness versus um, you know, more spastic muscles like in terms of bladder and bowel issues or sensation issues or issues, um, you know, with the face or anything like that? Dr. Pardo?
- Dr. Pardo: 00:07:40 So very good question. So one of the main characteristics of acute flaccid myelitis, as I mentioned before, is number one, is frequently, if not almost, it's frequently preceded by an upper respiratory infection, and the upper respiratory infection may go from a few days, and immediately after that respiratory infection, children develop this acute flaccid myelitis. The other difference, as compared with other autoimmune disorders that affect the spinal cord, is most of the time the illness affects children up to ages of 15 or even 18 years of age. Acute flaccid myelitis is very rare in adults. Also, there has been description of adults that have been affected by syndromes that are very similar to acute flaccid myelitis, but in general, the concept, the most general concept is that acute flaccid myelitis is a disease that affects mostly children. Now the other thing that is extremely important to understand is that in addition to the onset of weakness and the onset of some, uh, difficulties with movement, some children actually present with symptoms of what we call bulbar dysfunction. Let me explain, that is basically

lack of strength in the muscle groups that control face or control oral pharyngeal muscles. And many of these patients actually develop symptoms of respiratory distress, and some of these patients also develop symptoms of facial paralysis. So it's a combination of different areas of involvement in the spinal cord and areas of involvement of an area of the brain that we call, uh, brainstem, that is basically the bridge between the brain hemispheres and the spinal cord. So those are the main characteristics of a clinical presentation in this disorder.

- GG deFiebre: 00:10:05 Okay. Thank you. Um, and a lot of news stories have been referring to AFM as polio-like. Dr. Greenberg, can you talk a little bit about why this is, how it's being referred and how it's different from polio?
- Dr. Greenberg: 00:10:21 Yeah, and I think it's worth noting that the original clinical terminology polio myelitis is a language that is rooted in describing a syndrome, and the syndrome is when there is inflammation of the gray matter of the spinal cord leading to flaccid weakness. When the virus that was responsible for the majority of those cases was identified in the early 19 hundreds, the virus then got the name "the polio virus" because of its association with the syndrome. And over time, uh, decades, we learned to just associate the two; that poliomyelitis, flaccid weakness, was a condition seen by the polio virus. When in reality, the flaccid myelitis, in some places it's referred to as acute flaccid paralysis, it's been referred to as Landry's paralysis, it's been referred to as poliomyelitis. There's dozens of names in the literature to describe this syndrome of gray matter damage, presumably from a virus.
- Dr. Greenberg: 00:11:39 We know that there are multiple viruses beyond the polio virus that can cause this type of damage, where they differ is in their virulence, in their prevalence, and in, uh, the frequency with which they cause disease in humans. And so acute flaccid myelitis, clinically, is extremely similar to poliomyelitis based on what part of the spinal cord internally gets affected. But the poliomyelitis syndrome from the polio virus has several different features. The polio virus, when it causes paralysis, tends to cause paralysis more in the leg than the arms, and in what we've seen most recently in 2014, 2016, and this year, with the current acute flaccid myelitis outbreak, is a predominance of paralysis in the arms instead of the legs, although it can be both. In the setting of a polio virus outbreak in an unvaccinated population, uh, anywhere from one in 100 to one in a thousand people who get infected with the polio virus

will develop a paralytic condition again, in an unvaccinated population.

- Dr. Greenberg: 00:12:56 Whereas in the setting of acute flaccid myelitis, I know we're going to talk about causation, but the thinking is that the virus that may be responsible for the majority of these cases, the frequency with which an infected individual becomes paralyzed is far lower than what happens with the polio virus. And so the language is confusing. People will look up and say, "Geez, this looks just like polio." And the answer is yes, from a clinical syndrome perspective, but it does not look like the pattern epidemiologically that we see from the actual polio virus. And so there is a lot of work being done, and I don't know if we'll be able to talk about it, relative to what's driving our current numbers. It's, it's worth knowing that acute flaccid myelitis has been here for decades. Even once polio was eradicated from the United States, meaning a lack of a naturally occurring infection in the United States, which has been that way for many decades, uh, we have had children show up with acute flaccid myelitis, but in much smaller numbers. When we look back at our institution here in Dallas at Children's, we've had cases of acute flaccid myelitis. I moved here in 2009 and we've been documenting cases ever since I've been here. It's the number and the magnitude and the clustering that has changed in the recent several years.
- GG deFiebre: 00:14:25 Right. And so you kind of answered the next question I was going to ask, which was about whether AFM is new, and it sounds like it's not, it's just we're noticing it more because the numbers are higher. So just as a follow up to that, why does AFM tend to present in these sorts of clusters or um, you know, also, you know, every other year it seems to be since around 2014? Dr. Greenberg?
- Dr. Greenberg: 00:14:50 So the clustering is the cause of a lot of questions and a lot of research and a lot of work that needs to be done. I will speak for myself, um, in my interpretation of the data, and I'm very curious for Dr. Pardo to offer his views, is that what we're seeing in 2014, 2016, and 2018, I believe is related to specific circulating viruses, or in particular one particular virus. And over time, if you look at the last 50 years, this virus has changed genetically and has changed in prevalence within the United States. It was a virus that was hardly seen in the 1960s, -70's, -80's. There were some cases in the early 2000's reported of respiratory infections from this virus. And then as we got to 2014, when there was a much larger outbreak of this virus from

a respiratory perspective, it coincided with the first true outbreak of AFM cases.

- Dr. Greenberg: 00:15:58 And this virus seems to reappear from a respiratory infection perspective every other year in the United States. And indeed every other year from 2014, 2016 and 2018, we're seeing these outbreaks of acute flaccid myelitis. So I think the clustering represents the spread of the virus in larger metropolitan areas or areas where there is significant spread of this very common, very benign for the majority of people, respiratory virus. An unfortunate select few individuals, um, the virus is able to invade the nervous system and cause this condition, acute flaccid myelitis. But my read of the data is that this is linked to a particular virus or very narrow family of viruses that is emerging with a new neuro-virulence, ability to cause this syndrome of weakness. Um, Carlos, uh, what, what are your thoughts on this?
- Dr. Pardo: 00:16:55 So I think that I agree completely with your statements and introduction to this question. And I think that I will expand a little bit on that topic. So I will re-emphasize that acute flaccid myelitis is nothing new. And we already know after reviewing a characteristic of acute myelitis or acute paralysis in different centers, not only in the United States, but actually in many areas of the world. So the concept that this is a new disorder or new illness probably is not necessarily correct. But the second thing that is very fascinating is why acute flaccid myelitis is showing up in clusters, and I will introduce the topic of viruses, and viruses in general have coexisted with human beings all our lives. In other words, we basically developed as humans and viruses were already there. So very likely the interaction between the human beings and viruses has been there forever. The problem is that viruses, in the same way that many other organisms, viruses have different species and different families, and many of those different species and families adapt to different environments and have a capability of transmission and spreading that is directly related with their environment.
- Dr. Pardo: 00:18:27 So when viruses change, they also spread, and the magnitude of that spreading and change depends on many genetic factors. So it's very likely that the virus that is involved in acute flaccid myelitis has been dormant somewhere around the world, and it came and established in some areas of the United States at some point because, as Dr. Greenberg mentioned, may have been mutated or may have been genetically altered, and then spread to different populations that were susceptible to the virus because they were not exposed previously to that virus. In

other words, when we encounter a virus, we develop an ability to fight the virus and control the proliferation of the virus and the transmission of the virus. But it's very likely that the newest strain or the virus that's associated with acute flaccid myelitis was not recognized by the population in the United States in years before. And that's the reason it's encountering patients that have less ability to fight the virus.

Dr. Pardo: 00:19:45 So the reason it showed up initially in California and Colorado in 2014 and later spread to other states in the United States in 2016 and now is practically in all the United States is because the virus is following the typical patterns of viral spreading and transmission in which the virus requires not only environmental factors that facilitated transmission of the virus but also a host, in this case humans, that are going to be susceptible to facilitate the transmission at that same time to maintain the survival of the virus. So in other words, what we are encountering is a relatively new, new strain of virus and a new population that is not immune to that virus and that's the reason children are frequently affected. So that's the reason adults are not affected because we, as an adult, we already may have encountered some species of this or similar viruses and we are not susceptible to the new virus.

Dr. Pardo: 00:20:53 So we are resistant because our immune system has capability to fight that virus, but children don't. And that's the reason we are seeing these rare cases of acute flaccid myelitis, particularly in children that are more susceptible to these viral infections. So the next question that we need to ask is, all right, so the problem is that the virus is coming into the spinal cord and producing damage, or is that the immunological response toward the virus is producing damage of the gray matter of the spinal cord? Those are the two major questions that we need to answer in the next several months.

GG deFiebre: 00:21:37 Got it, thank you. And so, what do we understand about whether these viruses themselves are causing spinal cord damage or whether it's just an immune response that's responsible for the damage? Dr. Pardo, can you follow up to that?

Dr. Pardo: 00:21:51 So, since 2014, many researchers around the country have been trying to isolate the virus that is producing acute flaccid myelitis. And the basic standard for demonstrating that the virus is invading the central nervous system or the spinal cord is isolating the virus from either the spinal cord itself or from the spinal fluid. That is the fluid that is covering all of our brain and

the spinal cord. That attempt to demonstrate the presence of the virus in cerebrospinal fluid has failed dramatically. In other words, in very, very rare cases, the virus has been isolated from the spinal fluid. And in the majority of cases, the only association that we have been able to establish is the respiratory secretion or pharyngeal secretions are the only sources in which we are able to demonstrate presence of viruses. The viruses that we are talking about is called enterovirus. And enterovirus, actually it's a name that may be misleading because enterovirus may suggest that it's exclusively a virus of the gastrointestinal system, and that's not necessarily correct.

Dr. Pardo: 00:23:13 Enteroviruses in general are viruses that may affect different organs including the upper respiratory organs. And most of our patients with acute transverse myelitis actually develop upper respiratory infections, and the association with enterovirus has been exposed just because it's the only area of the body where we have been able to isolate those viruses. And there is one virus that is particularly concerning is enterovirus D68. That's the virus that has been postulated to be involved in presence of the majority of cases of acute flaccid myelitis. However, there are other viruses in the same family of enterovirus, like an enterovirus that is called A (as in apple) 71 that has been involved in presence of meningitis, encephalitis, and also acute flaccid myelitis. Recently, for example, in Colorado, there was a demonstration that some of those patients with acute flaccid myelitis were experiencing problems with enterovirus A71.

Dr. Pardo: 00:24:29 So the fact is that at this moment, we don't have direct evidence that the virus is going and directly attacking the spinal cord. We don't have such evidence yet. The evidence that we have is indirect evidence by the studies of the magnetic resonance imaging of the spinal cord that demonstrate the damage of the great matter. So, the suspect number one obviously is that the virus may be attacking directly the great matter, but the other possibility is that the immunological reaction that children are developing to this enterovirus or these viruses that are associated with the upper respiratory infection may be reacting in a very abnormal way and producing damage of the gray matter of the spinal cord in a very diffused pattern. So again, we have two major questions that we are not able to answer yet, is if the virus is coming and directly damaging the gray matter, or if the immune response, as the result of that infection, is responsible for that damage of the gray matter.

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- GG deFiebre: 00:25:46 Thank you. Um, and then Dr. Greenberg, is there any link that we found between AFM and vaccines?
- Dr. Greenberg: 00:25:56 Uh, so the short answer is no. So, and there've been a couple of different discussions that have gone on, um, whether it be in the literature or in data that's posted from the different research groups or even in forums on, on Facebook and things like that. One of the questions that came up early on was whether or not we were actually seeing polio virus occurring in unvaccinated individuals or individuals vaccinated with one version of the polio virus called the oral polio virus, which really isn't used in the United States anymore. And the answer was basically no, we, we've been unable to identify polio virus in any of the children who have had this condition in 2014, '16, or '18. And the overwhelming majority of these children have had their full vaccination schedule and are protected and have neutralizing antibodies to the polio virus. The flip side of the question has been asked, and that is, is there any relationship between vaccination status and developing acute flaccid myelitis, meaning are vaccines a risk factor? And the data so far says no. The overwhelming number of children who have gotten AFM have had no recent vaccination of any kind or vaccine exposure. These cases over these years have been happening before flu season and flu vaccination starts, which is one of the questions that comes up, and there hasn't been any pattern to vaccine exposure of any kind and developing AFM. So, so far we cannot find a link between the two.
- GG deFiebre: 00:27:33 Okay thank you. And then, in terms of how people present and coming to a diagnosis, is inflammation of the optic nerve or vision loss or issues with vision something that can happen with AFM, Dr. Greenberg?
- Dr. Greenberg: 00:27:46 That would be unusual in our experience. The overwhelming majority of cases have spinal cord focus inflammation. As Carlos mentioned, there are definitely children who have involvement of the brain stem, usually the lower brain stem, that can lead to facial weakness or swallowing issues. But an optic nerve involvement would be something that we would find highly unusual for the AFM syndrome. It is worth noting that at least at our center, we've had two cases where initially the syndrome looked like AFM and we've found an underlying auto antibody in those patients, and at least one of them did end up having optic nerve involvement. So if there are atypical features for acute flaccid myelitis, then it's incumbent upon clinicians and families to ensure that the diagnosis is accurate. But an optic nerve involvement, at least in our hands, would be very

unusual. Carlos, do you have experience that would be different than that? Are you seeing any cases with optic nerve involvement?

Dr. Pardo: 00:28:52

No, no, I agree with you. When you see optic neuritis, that is actually a flag, and probably you may need to reevaluate the diagnosis of acute flaccid myelitis. In the cases that we have served between 2015 and now, we haven't seen a definite involvement of the optic nerve. We have seen a facial paralysis and some of the lower cranial nerves but not optic neuritis.

GG deFiebre: 00:29:19

Okay. Thank you. And then also, I know that we talked previously about upper motor neuron and lower motor neuron. But does anyone with AFM present with both upper and lower motor neuron damage as well as anterior demyelination? Someone asked, this person has been diagnosed with idiopathic TM but is wondering whether it may actually be AFM.

Dr. Greenberg: 00:29:43

Yeah, if it's okay, Carlos, I'd like to jump in on that one because this is something we're spending a lot of time on. In our experience here, the answer is a definitive yes that there are patients who would meet the criteria for AFM, meaning they have a predominant amount of damage, a predilection of damage for those anterior horn cells, the gray matter, the lower motor neurons, leading to flaccid weakness, but who also have concomitantly inflammation and damage happening to the white matter and the tracks. So the classic example of this, and we've seen lots of children and adults with this, is a site of inflammation within the cervical spinal cord and only the cervical spinal cord in the neck where there is both flaccid weakness of the arms, because that gray matter in the neck was affected, but then there is also weakness of the legs associated with increased tone because the white matter in the neck was affected causing disruption of those wires that were on their way down to the legs, those upper motor neurons.

Dr. Greenberg: 00:30:57

And the reason the recognition of this phenomenon is important, and in those patients it's worth noting, they can have sensory changes and bowel/bladder changes to degree that's different than the AFM patients where the damage is only in the gray matter and restricted to the gray matter. In the cases where there's damage to both, our approach therapeutically to those patients has been different than if the gray matter is the only site of damage. And the theory that we're operating under is that there may be a viral infection of the anterior horns causing cell death and damage of those lower motor neurons, but that viral infection might elicit an immune response, and

that immune response may be responsible independently for additional damage to the spinal cord. If indeed that is the case, then the addition of anti-inflammatory therapies, whether they be steroids or IVIG or plasmapheresis, may be useful in salvaging the white matter even if it is not helping the gray matter. So, sorting out which patients have just gray matter involvement versus a mix of gray and white matter involvement is something we are particularly interested in here at our center.

GG deFiebre: 00:32:21 Okay, and to transition, I think that's a good transition to talk about treatments. So we've been keeping track of what the CDC has been saying about treatments, which is that they currently don't recommend treatments, but we know from speaking with you two and other medical professionals that some treatments are being used in AFM. So, Dr. Greenberg, do you mind just talking about what these treatments are, are they effective, are there any risks or benefits for these treatments in kids and adults with AFM?

Dr. Greenberg: 00:32:54 So, I'm definitely not going to do this one alone, so Carlos get ready, I'm going to want you to comment as well. This has been the source of, I think it's fair to say, a lot of controversy. And I want to first give background about why it's controversial, because I actually think it's important regardless of what our personal views are, and I have very biased personal views and I'm going to share them. It is worth noting that we have an absence of robust data, which means we are all trying to do the best we can with our recommendations. And so when different groups or individuals, and there are a diversity of opinions, disagree on the recommendations made, they may have the best of intentions for the recommendations, whether we, myself included, are right or wrong, but I will explain what my read of the data is. There is a theoretical concern that has been espoused and was part of treatment recommendations from colleagues at the Centers for Disease Control back in 2014 that raise concerns about using anti-inflammatory therapies such as steroids or plasmapheresis in the setting of acute flaccid myelitis, because if the injury was caused by a viral infection of the spinal cord, the theoretical concern was that the introduction of steroids or plasma exchange might make it harder for the body to fight the virus and things might get worse.

Dr. Greenberg: 00:34:27 We have taken a different view and approach. In our read, in the setting of infections and central nervous system, there is data both in the setting of encephalitis and meningitis and all

sorts of viral and bacterial infections of the central nervous system, that the risk of use of steroids in those situations seems to be extremely low. And in many patients, there seems to be a benefit. Likewise, the use of plasmapheresis in the setting of individuals who have an ongoing infection has not seemed to worsen the infection. So at our center, if there is evidence of that white matter involvement, that it's not just the gray matter, we have used steroids and plasmapheresis in an attempt to salvage the part of the spinal cord that we theorize is being damaged by the immune response and not by the virus directly. When we did an analysis of about 20 to 30 patients treated in this manner that we had seen in our clinic, the overwhelming majority of patients who got combination of steroids and plasmapheresis improved over time, and we could not document a clear association with a worse outcome for sure by using those means.

Dr. Greenberg: 00:35:49 The other agent that gets used in AFM quite a bit is intravenous immunoglobulin, which is basically a large pool of antibodies. And the theory is that the IVIG, the immunoglobulin may both help reduce inflammation and possibly help fight the infection if there are circulating antiviral antibodies in there. Our view here is that we don't think there's risks of the IVIG, we're not sure if we can quantify the benefit, but we absolutely have used it in situations where we thought it was prudent. To date, there has not been any agent that has been shown to have an antiviral capability, whether it be any of the commercially available antivirals or, at one time there was an examination of the use of high doses of PROZAC for antiviral capabilities. None of these, relative to the circulating enterovirus we're interested in, have been proven to change viral replication. So we have focused on the immunotherapy and then very quickly focusing on the rehabilitation because we are seeing improvement in kids, but it is mainly in the kids who are the most aggressive with their therapy approach. Carlos, I'm very curious to hear your thoughts on this.

Dr. Pardo: 00:37:20 This is a podcast, and a lot of people are involved in listening to our views, and what I need to make emphasis is, at this moment, we know that we don't have a specific treatment for acute flaccid myelitis. So our opinion is an antidotal opinion, and unfortunately as many rare diseases, it's extremely, extremely difficult to achieve a very serious analysis of data related with outcome after treatment. So in our experience here on the Northeast with the patients that we have seen between 2014 and 2018, our conclusion is unfortunately none of the treatments that we have used have been able to

demonstrate efficacy in preventing the rapid development of the neurological syndrome. So unfortunately, I need to say that I'm a little bit more conservative on the treatment approach. And I will say that at this moment we don't have a standard of care, a standard of treatment, and what we are doing is basically empirical treatment based on our experience with other types of spinal cord disorders.

Dr. Pardo: 00:38:40 So in our experience, for example, when we do the analysis of the involvement of the gray matter versus white matter, in our view, most of the damage, most of the involvement is the gray matter. And unfortunately, when patients arrive to our intensive care units, many of the patients have already experienced very, very extensive damage of the spinal cord. And one of our approaches right now is try to minimize the perpetuation of the immunological reaction by using IVIG. Our retrospective analysis of use of steroid treatment and plasma exchange has not been very positive, but again, you need to take in account that we are dealing with different characteristics of the disease as compared with other immunological problems of the spinal cord. So, I will say that our next challenge as healthcare providers for patients with acute flaccid myelitis is to get our data together and do a real analysis of those observations because as Dr. Greenberg stated, the observation that he has are, are very important, particularly when he has evaluated the magnitude of involvement of the gray matter versus white matter.

Dr. Pardo: 00:40:15 But when we do the same analysis in other areas of the country, the message that we are hearing is that the majority of the patients actually are not able to gain too much with the use of any of the three treatments that we are using, like plasma exchange, IV steroids, or even IVIG. So we're still on ground zero to achieve a very good or efficient treatment of acute flaccid myelitis. And I think that our role as scientists and healthcare providers in the next several months is try to come with better ideas and better approaches to have a good treatment for this illness. And perhaps the best approach is to get together and reanalyze all the data from all the centers around the United States that have been dealing with this illness, and see if we are able to come up with a more definite answer to that question.

Dr. Pardo: 00:41:20 So the other thing that is extremely important is the fact that we are not able to tackle the acute flaccid myelitis during the acute phase doesn't mean that we are basically losing the battle. I think that the most important is that we are more aware about these problems, that we already understand better

as compared with previous years the different types of complications that we are experiencing with patients with acute flaccid myelitis. Our intensive care doctors have a better understanding of the problems and are tackling the issue of the respiratory failure very efficiently. And the most important is, after the acute phase, there is a lot of things to do with the phase of neurological rehabilitation and intervention with physical therapy, occupational therapy, and the management of the mobility disorder that many of the children affected by acute flaccid myelitis are experiencing.

- GG deFiebre: 00:42:28 Okay, thank you. And then, relating to the CDC and their efforts at monitoring AFM. We, you know, we've gotten some questions from parents of children who have diagnosed, have been diagnosed with AFM by several neurologists, but you know, the CDC doesn't count them as part of a confirmed case. Dr. Greenberg, do you know anything about this or the difference between the case definition and the clinical definition might be?
- Dr. Greenberg: 00:43:01 Yeah. The source of a lot of controversy since 2014 and the cause of a lot of conversations with the CDC, which I need to say from the beginning are ongoing. For the record, I'll say I do not agree with everything that has come out of the CDC relative to AFM. I, however, firmly believe that the individuals working at the CDC are well intentioned individuals who are trying to get this right. And the role of being a public health official in the United States has a lot of complexity to it. I have no problem expressing my disagreement, however, when I do disagree and am working as many others, including Dr. Pardo and others, with them so that we can try and get this right. In order to do any epidemiologic study, ever, whether it's about lung cancer or AFM or heart attacks, one of the first steps is to set up a case definition. Who is going to be counted and who is not going to be counted in those statistics.
- Dr. Greenberg: 00:44:14 And in the beginning, it was clear to many of us that the case, the original case definition was too restrictive relative to acute flaccid myelitis. And the case definition has been going, undergoing revisions and is being evaluated even as we speak, to determine how we decide who gets counted and who doesn't. It is worth noting that the CDC relies on local and state health departments to assist in the reporting and classifying of conditions, and it is often state and local health departments that don't have adequate resources to screen or categorize different cases. And so, while a lot of the responsibility for organizing this firmly rests with the CDC, they do not control

every aspect of tracking this condition. And getting an accurate case definition is extremely important. And I'll give a couple examples. In 2014, the original case description said you had to be young, you had to be under 21 years of age, originally under 18 and then 21.

- Dr. Greenberg: 00:45:28 And we had multiple patients, not a lot but multiple who were over 21. And so we knew we were under counting. Secondly, the surveillance in 2014 really started in August. We had patients here in Dallas in June and July who didn't make it into the count, and so those numbers may be skewed. As we fast forward to 2018, this remains a voluntary reportable condition, meaning the public health officials of the United States and of different localities and states rely on clinicians not just to recognize the syndrome, but to alert the appropriate public health official and then provide a significant amount of data so a case determination can be made. If a clinician doesn't take the steps to report that case, then they will go uncounted relative to the CDC. And so there are a lot of complexities to this. The case definition is part of it, the need for better reporting is part of it. But there is a very valid concern that the numbers that are reported would underestimate and not overestimate the number of cases that are happening. I do not think it is a log fold or tenfold underestimate or underreporting, but I do think it is an underreporting.
- GG deFiebre: 00:46:51 Okay, thank you. And then, I'd like to talk a little bit about advocacy because we've gotten a few questions about that, and talk about the prognosis or long-term care for people with AFM. So, what's the best way for AFM families to advocate for more research or the best place to donate or, this is a question, who should we contact at the CDC? We got those three questions from, from someone who asked. So, Dr. Greenberg?
- Dr. Greenberg: 00:47:17 So, in terms of supporting research and advocacy, I give credit to the Transverse Myelitis Association, not just because, and in full disclosure, I am, as is Carlos and everybody here, members of the board and we play a role in advocacy and working with the Transverse Myelitis Association for advocacy. I give credit to the group because it has always been an organization that believes in a big tent philosophy, that if we combine patients with overlapping and critically tied syndromes - AFM as a variant to transverse myelitis, neuromyelitis optica, all these conditions - we are stronger together than if we parse out the, what are sometimes arbitrary lines. And so I know that the Transverse Myelitis Association, has, has been and continues to

be an advocate for acute flaccid myelitis families and is, I think, a great place to offer support.

- Dr. Greenberg: 00:48:17 Relative to trying to work with the CDC and public health officials, if there is an interest in increasing advocacy around this issue, this is one of those times where talking to your representative or your senator at the local, state, and federal level is actually useful. In what can often be a cynical world of politics, our congressional representatives and our US senators often really respond to families, more than organizations, families who are in their district and in their state coming to them and informing them and teaching them how this condition has impacted them as an individual and as a family. And then asking them to take action to advocate for nationally supported resources. We are going to need the help of the CDC. We're going to need to help of the NIH.
- Dr. Greenberg: 00:49:19 If we determine that there is a prevalent virus driving this, and if in years to come it doesn't go away and keeps doing what it's doing every other year, then there needs to be a legitimate, serious investment in a potential vaccination program and exploring what are the ways to eradicate this. And that's only gonna happen if there is federal level support. So from a grassroots perspective, I have a strong support for what the Transverse Myelitis Association does. And an advocacy perspective, I think everybody who has been affected by this can do a lot for the field by getting in touch with their representatives or senators and being a voice and being active and being a representative.
- GG deFiebre: 00:50:13 Thank you, Dr. Greenberg. And Dr. Pardo, what are you and Dr. Greenberg and your colleagues doing together to raise awareness and get diagnostic criteria and treatment info out to other medical professionals?
- Dr. Pardo: 00:50:25 So it's a very interesting question, and it's a continuation of what Dr. Greenberg was stating. And I think that the most important aspect of the role of the Transverse Myelitis Association, for example, is not only patient advocacy, but we have been a beneficiary of the support to get medical groups all together. And actually it's extremely important that all of you learn that we are working together with many colleagues around the country. So in the past couple of weeks, we got together with our colleagues in Minnesota. We got together with our colleagues in Wisconsin in Pennsylvania, in Massachusetts. We reached out to our colleagues in Colorado and Texas and California that had experience with this illness

before, and all together are basically working to establish a better understanding of acute flaccid myelitis. Let me give you an example. We are trying to understand the question that we had before. What is the proper treatment? What is the best way to diagnose acute flaccid myelitis? What is the best way to get biological samples to achieve a diagnosis?

Dr. Pardo: 00:51:47 What is the best way to get patients in rehabilitation? So we have been working in the past few weeks in a team effort that will come up with recommendations and guidelines that help all healthcare providers around the United States to deal with the acute flaccid myelitis because this is a problem that is not going away. It's very likely that this outbreak is going to be over in the next couple of months, and by February of 2019, very likely everybody will stop hearing about cases of acute flaccid myelitis. But forget it. We are going to see that same problem again in the next summer and perhaps in two or three or four more summers, and we are going to be dealing with exactly the same situation that we are dealing with right now. So the group of healthcare providers, physicians, scientists, and all people that have been supported by the Transverse Myelitis Association and all people that have been involved in the recent outbreaks of AFM are working together to provide a better understanding of this syndrome.

Dr. Pardo: 00:53:00 I will mention something that was mentioned before by Dr. Greenberg. CDC is a federal entity that is in charge of surveillance of neurological trauma, infectious problems, and health problems in general, but in many ways the responsibility to outline treatments, medical treatments is not a CDC. It's our own responsibility as a healthcare provider, as a specialist in neurology, as a specialist in infectious diseases, and a specialist in rehabilitation, it's our own responsibility to get together and provide those guidelines and those recommendations for future outbreaks for the management of patients with acute flaccid myelitis. So that's basically an important aspect of what the Transverse Myelitis Association and the physicians and the healthcare providers that are working with the Transverse Myelitis Association are doing currently in the middle of this outbreak.

GG deFiebre: 00:53:57 Thank you. And thank you both so much for your advocacy. You know, it's, it's really important. So for the last few minutes, I would like to talk about prognosis and ongoing care. So we got a lot of questions about what the prognosis is for, for someone diagnosed with AFM, and if there's any hope or anything being

researched now that might help repair the damage that was done? Dr. Greenberg?

- Dr. Greenberg: 00:54:27 So one of the things that is definitely worth noting, and as Carlos said, a lot of what's happening around the country comes from experience and different folks' experiences, is we're seeing improvement. It is slow but steady, but it is not happening spontaneously. So I have not seen a child who was affected either minimally or significantly from this condition all of a sudden spontaneously get back function of a limb. But what I have seen are children who when working with their families and just some really inspirational and impressive families, when they are very committed to daily repetition of therapies, we're seeing kids improve. We are using two modalities alongside of traditional therapy to try and push the improvement. At least at our center, we are still a believer that there may be a role for electrical stimulation of these muscle groups even if there is not an obvious muscle contraction.
- Dr. Greenberg: 00:55:34 And there is some data from animal work to suggest that that may help with reinnervation of a muscle that has lost its innervation. And the second is we are following children very closely, as I know our colleagues at Hopkins do as well, to identify children who may be a candidate for nerve transplant procedures to try and restore function to a limb or part of a limb that has lost innervation. And that requires watching children during their recovery, especially over that first 6 to 12 months, very carefully and deciding if there's a role for a transplantation procedure. But even in the absence of a surgical intervention, the families who are, and the kiddos who really get into a good regimen in terms of physical and occupational therapy, we are seeing them improve slow and steady. We have had multiple children who started off as a quadriplegic and ventilator dependent who are now walking and off ventilators, but it's not happening fast. It's going very slowly and just with a grueling amount of work and an extreme commitment to that schedule. But it works. With the investment, it looks as though it's paying off over a period of often years. Carlos, does that resonate with what you've seen or are we an outlier?
- Dr. Pardo: 00:56:58 No, I think that that's exactly what we have seen as well. So I think, I always encourage all our patients, not only with acute flaccid myelitis and their families, but also all the patients with transverse myelitis and acute neurological and chronic neurological problems. And the most important is the persistence and particularly the emphasis in the process of rehabilitation. We frequently are expecting magic solutions and

quick solutions, and unfortunately in neurological problems, those solutions don't exist. We need to rely in persistence and probably in better approaches for stimulation of the central nervous system to maintain a good degree of function of that central nervous system. And that is precisely what all of these techniques of electrical stimulation and rehabilitation are doing.

- Dr. Pardo: 00:57:59 So I definitely will encourage all our patients and families to be persistent. I mean the fact that the recovery is not happening in one week or two weeks doesn't mean that there is not going to be recovery. There is recovery, and that recovery may be slow but can be achieved over weeks, months, and perhaps years of aggressive process of rehabilitation and therapy. Technologies are moving very quickly, and it is very likely in the next few months and years, we are going to see better progress in improving mobility and motor function of many of our patients with acute flaccid myelitis. So that's the reason it's extremely important to be persistent in this process.
- GG deFiebre: 00:58:44 Thank you. And as we are nearing the end of our time, do either of you have any last comments or things that we didn't cover that you think we should mention?
- Dr. Greenberg: 00:58:55 I think we covered a lot of ground, and this is an issue that's not going away. And for the families who have been affected by this, I just want them to know that there are a lot of us who are very committed to trying to find better therapies and improve outcomes for your children and your loved ones. And we partner with the TMA to try and achieve that goal, and at the same time we partner with colleagues across the country so that we can prevent this from happening to kids in the future. It's a lot of work to be done, but I firmly believe we're going to get there.
- Dr. Pardo: 00:59:44 And I need to emphasize that there are a lot of healthcare providers around the country with very good expertise, not only in neurology but also in rehabilitation and other areas of that are involved in transverse myelitis and myelitis in general. So we have the UT Southwestern Transverse Myelitis Center. We have a new Transverse Myelitis Center in Cincinnati. We have a group in Salt Lake in Utah working actively in myelitis. We have colleagues in Boston who are also very interested in myelitis. We have the Johns Hopkins Transverse Myelitis Center. So there are people with expertise in myelitis in different areas of the country that are available and ready to help if that help is needed.

The Transverse Myelitis Association 'Ask the Expert' Podcast Series
2018 Podcast on Acute Flaccid Myelitis

GG deFiebre:	01:00:23	Thank you. And I just want to thank you both so much for your leadership and compassion and commitment to our families and our community. It really means a lot to us. So yes, we really thank you for that.
Dr. Pardo:	01:00:38	Thank you GG.
Dr. Greenberg:	01:00:42	Thank you.
Dr. Pardo:	01:00:42	And thank you to all of the participants in this podcast.
GG deFiebre:	01:00:43	Thank you. Yes, and we'll continue this conversation with future podcasts and additional resources as we get more information. And this, again, has been recorded and will be made available on our website. So thank you so much.
Dr. Pardo:	01:00:59	Thank you.
Dr. Greenberg:	01:00:59	Thank you.