A Virtual Townhall Forum: 2021 AFM Diagnostic Criteria and Management

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Dr. Carlos Pardo: [00:00:00] Thank you very much, all of you, for joining the Acute Flaccid Myelitis Working Group. This is the first meeting of the year. Hopefully 2021 is going to be a better year after this difficult situation that we have experienced with COVID 19. Hopefully all of you are safe and doing well. The main goal of the meeting today is a virtual forum on the diagnosis of acute flaccid myelitis.

[00:00:29] We have a good opportunity to discuss in the past several months about how to achieve a better diagnosis of acute flaccid myelitis and how to focus on improving the clinical diagnosis and management. So the main goal of this meeting today is more educational, in, in many ways, just to bring everybody to the criteria that were outlined in the paper published recently in Landset. The four topics that we are going to discuss is, number one is just an outline of the diagnostic criteria. The second topic is extremely important, is how we are going to use these diagnostic criteria in the clinicalogical setting.

[00:01:17] What is the importance of acute flaccid myelitis criteria in research, both clinical research and basic science research? I will open briefly the discussion about consensus of management. Also, I don't believe that the time will allow us to discuss extensively on these topics, but if we are able to share for at least an initial discussion about management in the emergency situation and critical care, that will be fine. But this is a big, big topic that probably is going to be difficult to be covered just during this period of one and a half hour.

[00:01:56] So, again, the panel is here. Many of them participated in the discussion about the diagnostic criteria. And what I like to do is I like to ask Olwen, who is in the audience, to walk us through the different elements of the diagnostic criteria, and what was the purpose of these criteria. Olwen?

Dr. Olwen Murphy: [00:02:22] Sure. Thanks for that, Carlos. So this is the diagnostic criteria that took some time and a lot of expert opinion for us to reach a consensus on. There's a couple of components that we felt were important to include.

[00:02:37] So you can see that the diagnostic items are laddered. There's H, there's E, there's MRI and CSF. So the H refers to the elements of the clinical history that are important in the diagnosis of AFM. So H is an acute onset of limb weakness. Based on published data, we identified that the period from the onset of the illness to the neurological, to the most severe neurological weakness falls within hours to 10 days. So that seems to be a good discriminating factor, to some extent, on what's AFM versus other causes of paralysis.

[00:03:16] The second element of the history is the presence of a prodromal illness. So that's prior to the onset of neurological weakness, whether there's fever, whether there's a viral illness, like a cough, cold, respiratory symptoms, wheeze, sometimes gastrointestinal symptoms as well.

[00:03:37] Then we move on to the elements of the examination findings that can support a diagnosis of AFM. The first is weakness, of course, the key part of the, the presentation of AFM. And we know that this can involve the limbs, it can involve the neck, the face, or the cranial nerves or the muscles of the trunk. So the presence of weakness in these areas is a requisite for diagnosis of AFM.

[00:04:03] Next is the type of weakness. So AFM we know is a flaccid disease. So typically in, in the acute phase, children or affected people have flaccid weakness. So we describe this as decreased muscle tone and at least one weak limb. And then the third element of the examination findings that are useful for the diagnosis of AFM are decreased or absent tendon reflexes and at least one week later.

[00:04:32] And it's going to help differentiate us from other causes of spinal cord disorders, which often manifest with increased reflexes. On the MRI, this is a really helpful diagnostic tool in identifying AFM. And the spinal cord lesions that we typically see in AFM predominantly affect the gray matter.

[00:04:55] And there tends to not be enhancement of the gray matter itself, but often there can be nerve root enhancement of the nerve roots that are exiting, particularly the dorsal or posterior gray matter. And then in terms of the, the CSF findings, we tend to see a pleocytosis, which is an increased white cell count of more than five cells per liter. And this, again, can be helpful in diagnosing AFM.

[00:05:24] So, as we know in clinical medicine, there's a lot of nuances and subtleties in how different individuals can present. So some children may have this full host of findings and be very characteristic of all elements of AFM. And then in other affected people, there may be a little bit more uncertainty in terms of making a diagnosis. So there's a couple of categories here. So there's a definitite, probable, possible, or uncertain. And this can really help us, help us in terms of firstly, tracking the disease in different countries over different time periods, and secondly, in terms of the clinical research. So for example, if someone's completing a research study on prognosis and AFM, on viral aspects of the disease, it can help that we can define cases to term based on the certainty of the diagnosis. So essentially, the way the diagnostic criteria here are designed is that to have a definite diagnosis of AFM, you really have to have all these elements of the diagnostic criteria except for the presence of the prodromal fever or illness. While this is a helpful pointer, we do, we do know that there's certain children, and particularly young children, where there may not be a clearly apparent prodromal illness. So we did not want to exclude those patients from having a certain diagnosis of AFM.

[00:06:50] Then the probable category is mainly taking count of the patients in whom there's no CSF pleocytosis or else they didn't have a CSF study in the early phase of the disease. We know that the pleocytosis seems to be most marked in the first week to two weeks of the infection. So we do frequently encounter patients where they present maybe a few weeks later, or maybe another diagnosis is considered initially and they're only attending a few months down the line when it becomes apparent that the initial diagnosis was incorrect, and they may not have had the CSF for that reason. So again, this probable diagnostic category takes account of those patients.

[00:07:32] Next is the possible category. This is taking account of really the patients that they don't have all of the clearcut elements of the clinical presentation. So they have to have some elements. So they have to have some kind of weakness. It doesn't need to be in the limbs. So it could just be a cranial nerve presentation, for example, patients with a weakness of swallow or speech or their neck weakness, for example. We do see some of these cases with the more sort of limited presentation. It's a little bit more difficult to make the diagnosis in these cases, which is why we've categorized them as possible. Otherwise, that diagnostic category is quite similar to the, to the probable category.

[00:08:14] And finally, we have the uncertain diagnostic category. This is really a category that takes account of the patient who has a clear, a clinical syndrome consistent with AFM. So all the elements of the history and examination that we would expect in AFM are present, but they may not have had the appropriate investigations at the appropriate time. It's maybe because region has limited resources and does not have the availability of MRI and CSF testing acutely. Or it may be for another reason, like a misdiagnosis initially. For example, with Guillain-Barre syndrome and perhaps an MRI and CSF study were not done at the onset of the disease.

[00:08:53] So these kinds of categories we think should be helpful for clinical researchers, and particularly in terms of defining the certainty of the diagnosis. And then finally, as we can see at the bottom of the diagnostic criteria, we have outlined a number of factors that may point you away from AFM or may point the doctors away from AFM and towards another type of diagnosis. So the first would be encephalopathy. So if a patient is obtunded, comatose, or very confused, this would be unusual for AFM. Secondly would be the presence of sensory deficits on the examination. So if there's loss of proprioception, for example, vibration, sensation, or clear sensory level. This would be not a characteristic of AFM.

[00:09:42] Next would be the presence of lesions, essentially in the, in the brain, in the white matter, or the cortex, which would be very unusual for AFM. We do sometimes see deep gray matter lesions, but not in the, the supratentorial white matter or cortex. It would be much more characteristic of other type of neuroinflammatory diseases that can mimmick AFM.

[00:10:05] And then patients without CSF pleocytosis can be a little bit more nuanced, and it's important in those patients to consider other things like Guillain-Barre syndrome. Positive aquaporin-4 antibody is not consistent with AFM, and it's suggestive of a diagnosis of neuromyelitis optica spectrum disorder. And a positive sero-MOG antibody, particularly at a high titer, is very suggestive of MOG antibody-associated disease. And again, it's not consistent with AFM. So I guess I'll hand back to Carlos then.

Dr. Carlos Pardo: [00:10:40] Thank you, Olwen. That was a very good overview of the criteria. Now, when we use diagnostic criteria, it's because we need to be very certain that we establish a good diagnosis for management.

[00:10:53] And one of the difficult parts in the evaluation of patients with acute weakness is that there are different set of disorders that we encounter that may mimic acute flaccid myelitis, and we need to be really very certain that we establish the right diagnosis. So I will invite two of my colleagues here, is Dr. Ben Greenberg and Dr. Matt Elric. And I will start with Ben asking, give us a very good view of what the clinician, the pediatrician needs to be aware of when we are dealing with a diagnosis of acute flaccid myelitis versus the diagnosis of t ansverse myelitis or the diagnosis of spinal cord infarct.

Dr. Benjamin Greenberg: [00:11:37] Well so clinically, as I think has been alluded to, there can be significant overlap. And I, I think the major red flag, clinically, that we look for to put people into, children into a category of acute flaccid myelitis is flaccid weakness of one or more limbs. So that not only is the limb not mobile, but it's loose and that there are reduced reflexes. But it is important to recognize that some children with acute flaccid myelitis can have a mixed picture where, for example, the arms may be flaccid, but they may actually have upper motor neuron signs of weakness in the legs where the tone has actually increased, which is the classic finding for the historically described transverse myelitis. So, at a minimum, there needs to be one or more limbs with flaccid weakness.

[00:12:30] If none of the limbs are flaccid, if all of the weakness is with increased tone, then it drops the probability of it being acute flaccid myelitis. It's not impossible, but it drops it significantly. So the pattern of weakness is critical. The timing is critical. And then we put that history and that physical and the imaging

and everything that was discussed together to try and put kids into that proper category. But in about half approximately of our children we've diagnosed with acute flaccid myelitis, we can have findings in some limbs of weakness that isn't flaccid.

Dr. Carlos Pardo: [00:13:08] Thank you, Ben. That's a very good overview. Matt, one of the major concerns that we deal in the emergency department with acute paralysis in children is Guillain-Barre. What are your recommendations as a pediatric neurologist when you are dealing with these situations in the emergency department, and what are the clues that you are going to advise the clinicians and healthcare providers about the differentiation between Guillain-Barre and acute flaccid myelitis?

Dr. Matt Elric: [00:13:39] Sure. So, in both cases, the, the presentation is often acute onset of flaccid weakness. The time course in Guillain-Barre syndrome is, on average, a little bit slower. So the onset might be more subtle and, and take more like weeks to, to really reach a nadir, but there's a lot of overlap in the, in the time course. So the onset can look very similar to AFM. In evaluating these kids in the emergency room, some of the other findings that might come up early would be a sensory deficit, which is very prominent in most forms of Guillain-Barre syndrome and would point you away from AFM.

[00:14:12] But in a lot of cases, the, there's a lot of overlap clinically before we do further investigation. Traditionally, before AFM became as common as it is, the, the diagnosis for Guillain-Barre syndrome would be to do simply a, a lumbar puncture and then make a diagnosis on that, on that basis alone, in which case the spinal fluid shows elevated protein with a typically normal cell count. So almost the inverse of what we see in AFM where the cell counts are very high, and the protein is, is normal or modestly elevated. The way that we typically approach this differential now is to go straight from our clinical exam to MRI, followed by LP, where we can put the two pieces of information together and differentiate AFM versus GBS.

[00:14:54] The spinal cord MRI in Guillain-Barre syndrome will show, the cord itself will be normal in contrast with, with AFM where you see the gray matter predominant T2 hyperintensity. In both cases, nerve root enhancement can be seen. In GBS, it's more commonly all roots, compared to ventral roots in AFM.

[00:15:13] Typically, the combination of those two studies done in the acute phase can, can place you in one category or the other.

Dr. Carlos Pardo: [00:15:20] Thank you, Matt. Matt, since you work in the EMG switch all the time, there is always some anxiety about doing EMGs and nerve conduction studies when you are looking for a possibility of Guillain-Barre or even acute flaccid myelitis.

[00:15:35] So what is your advice that you are giving to the emergency department clinicians or the clinician seeing patients with concerns about either Guillain-Barre or acute flaccid myelitis?

Dr. Matt Elric: [00:15:47] Yeah. In, in both cases, the typical findings on EMG take a period of time to evolve, even though the patient obviously is clinically weak right away. In the, in the early stage, really all you can see in, in either case is that the patient fails to activate the muscles, but the nerve conductions can remain normal, so you don't have a good explanation for why that is. As the disease evolves, you can see the classic findings that would point you towards one diagnosis or the other. In AFM, you see loss of the motor nerve conductions and signs of, of denervation on the, on the needle EMG, which points you towards a motor neuron apathy.

[00:16:21] One of the variants of Guillain-Barre syndrome called AMAN can, can sometimes look similar. But Guillain-Barre will most often show you both the motor and sensory problem and, and often signs of demyelination, which are absent in AFM. We typically recommend waiting at least a week to do the EMG

so that you can see some typical findings, and often it takes two or three for, for really clear characteristic findings to emerge in either case. So the EMG is not recommended as a part of the acute workup for AFM. But if there's diagnostic uncertainty that remains after the, the typical evaluation, doing that study a week or more after onset of weakness can be helpful.

Dr. Carlos Pardo: [00:16:58] Thank you, Matt. So I will ask Kevin, and later I will ask Catherine Otten and Grace their opinion about their experiences in the clinical setting. But first, with Kevin. So, obviously, in the emergency department, it's critical when we are evaluating patients, and then the next question is, okay, what, what are we going to do? What type of samples are we going to use?

[00:17:24] So, when we are dealing with a different situation like AFM or Guillain-Barre, what would be your recommendation from infectious point of view, as an infectious specialist, what would you recommend the clinician in the emergency department?

Dr. Kevin Messacar: [00:17:38] So I think that the keys are, as soon as you suspect AFM, even if it's not confirmed, the prompt collection of specimens is really key. Because what we know as far as detecting pathogen is that it's likely fleeting, so it likely happens early. As we just heard from Olwen, there's a significant natural delay in presentation from the prodromal illness to the neurologic onset. So we're already behind the clock typically, even if a patient is diagnosed right away. So as soon as AFM is suspected, we'd recommend broad specimen collection, looking at all of the sites that the viruses that have been associated with it could be shed.

[00:18:19] So that includes the nasal pharynx, so that's the brain tickler, the deep nasal sample; oral pharyngeal, so that's a throat swab; a blood sample; a CSF sample, as we talked about; and then either a stool sample, if you can collect it, although clinically many of these patients present with constipation, so we often recommend getting a rectal swab if you're waiting for a stool and that that can be collected more promptly.

[00:18:45] And as far as clinical testing that can be done on site, obviously you run what you can at your institution. But the public health side can also assist, and talking to your state health department, reporting the case, and getting those samples to the CDC where specialized testing can occur really helps us to better understand the condition at a larger level.

Dr. Carlos Pardo: [00:19:05] Thank you, Kevin. And, and Catherine and Grace, in your experience, you are basically working in the two different corners of, of the United States. So, tell us your experience about evaluating these patients in the acute setting and, and the difficulties that clinicians may encounter evaluating these patients.

Dr. Catherine Otten: [00:19:26] Ah, I can go first, up in, up in the upper left corner. I think our biggest reminder for clinicians seeing these patients is just to keep it on the differential because it certainly isn't going to be the first thing that folks will think of when they think of weakness. But also to keep in mind that the initial MRI may actually not be as helpful as one, say, obtained 24 hours later, if symptoms are persistent. We do occasionally get patients who show up within hours of symptom onset, which is wonderful, but those early results can sometimes be misleading.

[00:19:59] We haven't found that we're capable of getting an LP quite as quickly as an MRI. So I think we've had a higher yield in identifying inflammation on the lumbar puncture than we have on the MRI, which is often done very quickly, especially since ischemia is often on that early differential.

Dr. Carlos Pardo: [00:20:19] Thank you, Catherine. Grace? Not sure if Grace is mute.

Dr. Grace Gombolay: [00:20:23] Hello, everyone. Sorry about that, I think I was on mute. Yes, evaluating these patients can be kind of tricky sometimes, especially in the initial phase. But we definitely try to get all the evaluations done, including MRI, spinal fluid, and all of those things.

Dr. Carlos Pardo: [00:20:39] So it's how is the interaction with the emergency department? I mean, you as a clinician, pediatric neurologist, interaction with the emergency department. Is that something that is hindering sometimes the quick assessment of these patients?

Dr. Grace Gombolay: [00:20:55] We've done a lot of education between our departments, including the ER, staff, to remind them, especially on years in which we predict we will see clusters. I think that's been very helpful and we are certainly getting actually a lot of consults for patients who don't have AFM because they're keeping it on the differential for patients in whom it's appropriate, even if it doesn't end up being the ultimate diagnosis. One issue we have had is, we serve a wide rural setting. And especially if a patient arrives in an ER more set up for adult patients, it just isn't something that's often on their differential. And doing a pediatric neurologic exam on a, on a toddler with strong feelings can sometimes be challenging for providers that are more used to adult patients.

[00:21:43] So I know there's been a lot more outreach and I'm, I'm interested to see how that changes as more and more people recognize this as, as something they have to consider and something that they have to transfer care often for, to get a more rapid specialized evaluation.

Dr. Carlos Pardo: [00:21:59] That's very helpful. And I think that probably one of the main messages is to establish very good connectivity with our colleagues in the pediatric emergency departments, because that is critical for expeditious assessment of all patients suspected to have acute flaccid myelitis or any type of acute neurological disorder.

[00:22:20] So, I'd like to open now the, a very interesting discussion that actually has been in the mind of everybody in the past few years with acute flaccid myelitis. The CDC has been helping us with surveillance of enterovirus circulation. And, and the criteria that was established initially for acute flaccid myelitis actually was driven by the work of the CDC. Sarah and Adriana are part of the CDC. They are here with us.

[00:22:54] And I'd like to invite them to give us their perspective about, now we have some criteria that may be somewhat different to the CDC criteria for AFM. And we'd liked that you explain to us and the audience about, what is the difference between diagnostic criteria for surveillance versus diagnostic criteria for clinical management. Because that is actually a very important distinction.

[00:23:21] And unfortunately, in the past, many families, parents, and even clinicians were with the belief that the CDC was establishing clinical diagnosis and confirming clinical diagnosis - assumption that is not really the role of the CDC. And so I will open the microphone to Adriana and Sarah to explain what, what do you think about the introduction of clinical criteria and what is the work that you are doing for surveillance?

Adriana Lopez, MHS: [00:23:50] Thank you, Carlos. Yeah and, and as you brought up, this has been an issue in communicating this to families. There's always confusion when they hear about the CDC case classification versus what their clinician is diagnosing. So that's something that we've been trying to message better and to make that distinction, that what we're doing at CDC is public health surveillance, which is done at the population level and uses the consistent and specific criteria for case classification to help us learn more about AFM by ensuring that the cases that we're tracking over time are similar. So, and that is on, on the other hand, we have the clinical diagnosis, which is used for patient level individual clinical management decisions and is more time sensitive.

[00:24:43] So we want to make it clear that surveillance is meant for disease tracking purposes and to learn more about it and should not have an effect on the clinical diagnosis given by the treating clinicians. So they should pretty much be separate. But with that said, our definitions are actually very similar.

[00:25:02] So, in looking at the criteria, the diagnostic criteria that you guys have come up with, which I think will be very helpful in terms of clinicians when they're seeing their patients, that, you know, all of the cases that you guys have listed as categorized in the definite and probable categories would be classified as confirmed cases under our surveillance definition.

[00:25:24] The main difference that we noticed between these two, between the surveillance and the clinical diagnostic criteria, is that our confirmed classification requires limb weakness, whereas the definite probable criteria may not necessarily have limb weakness but does include facial cranial nerve and neck weakness.

[00:25:47] So you could have somebody with neck weakness but no limb weakness that is classified as definite or probable with your criteria but would not necessarily be a confirmed case for surveillance purposes. Now, we don't know what the proportion of that will be, but it will be interesting to see now that we do have these criteria that we can compare moving forward.

[00:26:10] So that will be helpful in terms of learning more about, you know, what proportion of cases actually do present with no limb weakness. But with all that, you know, we're, we'll continue to count our cases as we have using our surveillance case definition. But, it is helpful to have this clinical diagnosis.

[00:26:30] Because what we can do with our surveillance data is then look more specifically at them and analyze it using the diagnostic criteria to see how many of our confirmed cases fall into the different categories, definite or probable. So, we're also going to be analyzing our surveillance data looking at more of a secondary clinical diagnosis or review, so that we'll have a better sense of the clinical diagnosis of these confirmed, or the cases that fall into our confirmed category.

Dr. Carlos Pardo: [00:27:03] Thank you, Adriana. Actually, there is one interesting topic of discussion today, and one of the questions that was submitted to the forum and, again, I, I'd like to remind the participants that you can send questions to the chat. So, we have the opportunity to discuss some of these questions. But one of the questions that Larry posted in the chat is, do we have any epidemiological signals that we should expect a surge of AFM in 2021?

[00:27:31] That would be off our cycle per se. Is there any evidence about circulation of rhinovirus or enterovirus? So what is the perspective from the CDC? The data is available about circulation or surge of enterovirus or other type of v ruses in the setting of COVID-19?

Adriana Lopez, MHS: [00:27:53] Sure. Unfortunately, we do not have national surveillance for enteroviruses, but CDC does conduct surveillance for enteroviruses in seven active prospective population-based network sites.

[00:28:08] And what they do is, these sites are used to look at acute respiratory illness in children less than 18 years of age. And kids who are hospitalized or visit emergency departments at these seven sites are enrolled. They test specimens and they type for EVD 68 specifically. And generally they're testing and collecting specimens from July through November of each year.

[00:28:32] So, looking at these data for 2020, we have preliminary data right now, but from the period of July through November, we have, sites did report some EV-D68 detections, but it was about 28 detections among

children. And, most of the sites had some detections. The highest number of detections occurred in October, whereas in 2018, our last peak year, more of the detections occurred in September.

[00:29:02] And in comparing what we're seeing this year to what we've seen in previous years, from July through November in 2019, there were only nine detections of EV-D68 compared to 2018 during that same period when there were 381 detections. So, there was some circulation of EV-D68 in 2020, but nothing compared to what we saw in 2018, a little more than what we saw, what we've seen in our non-peak years of 2019, and also 2017.

[00:29:35] One thing that was done this year - or in 2020, was to expand the testing through December to see if there was continued circulation of enteroviruses. The testing is not complete, but as of right now, there haven't been any detections. So it does seem like there were detections throughout these seven sites.

[00:29:56] There was one site that had more detections than the others. So it's interesting to think that it's possible that some of the non-pharmaceutical interventions that could have played a role in, you know, the detections that we did see.

Dr. Carlos Pardo: [00:30:10] Thanks, Adriana. I don't know if Sarah has anything else to add to the discussion of surveillance.

Dr. Sarah Kidd: [00:30:19] No. Thank you. Adriana was our designated spokesperson today. So I think she covered it very well.

Dr. Carlos Pardo: [00:30:24] Thank you, Sarah. And thank you for all your help with COVID-19. I know that you are quite busy there. This actually opens the opportunity to discuss another interesting topic, is the topic of, okay, we have some diagnostic criteria for acute flaccid myelitis.

[00:30:38] How is that going to impact the clinical research? We have been working very actively in the past several months with our colleagues David Kimberlin at the UAB and NIH. And the natural history study of AFM was launched last year. So, David, what is your view, how we are able to basically use all of these criteria emphasizing the correct diagnosis and actually make sure that the studies that we're launching for understanding the natural history of AFM are accomplished?

Dr. David Kimberlin: [00:31:14] Thank you, Carlos, and, and, and to the larger group as well, for the tremendous work y'all have put in. I think that, that the kind of structure that you all have put around the diagnostic criteria will only enhance the, the work coming out of this, this very large natural history study that, that so many of us are participating in.

[00:31:35] And the reason I say that is that as many of you know, this study is, has been designed from the beginning to sweep up as many potential AFM cases as possible. And then as data are gathered on each individual subject enrolled, there is an adjudication, you know, a handful of months down the road, to determine whether or not yes, in fact, that subject really had AFM, you know, proven, probable, possible, or whether something else had been ruled in, or it just flat out turned out not to be AFM.

[00:32:10] And, and, and so all of those efforts that will be undertaken by the adjudication committee really are not specified in the protocol or in the manual of procedures. And, and therefore having these kinds of structured criteria I think will make that process a more structured process. And that can only benefit that, that particular, number one, the study that we're working on.

[00:32:33] But, but really, I would suggest it would benefit, you know, all research in AFM going forward. Will there need to be adjustments to the, to the criteria? Perhaps. But it's better to use the same sort of diagnostic approach and then modify as needed and then use that newly modified diagnostic approach in a structured, systematic way, rather than just kind of everybody kind of using their own interpretation or their own judgment on it. So I, I view this as an incredibly positive step.

Dr. Carlos Pardo: [00:33:02] Thank you, David. And, just for information for the public, so far, how many sites are active now for the NIH study?

Dr. David Kimberlin: [00:33:13] Jill, do you have the total number? I know that all but one site are active and I think that puts us at about 30 or 35 total sites.

Jill Griffin, RN: [00:33:22] Actually, David, all of our US sites and [inaudible] sites are active. The only sites that are not active are in the UK.

Dr. David Kimberlin: [00:33:29] Got it.

Dr. Carlos Pardo: [00:33:30] Great. And, and, Jill and David, one thing that is important for, for the group and for the families and, audience is, frequently when we encounter patients in the ER, and actually we had that situation recently here in our institution, so there is a lot of anxiety about the clinical diagnosis, future management, et cetera. And sometimes families and parents are very hesitant to, to agree on committing to a research effort, particularly clinical research effort. What is the message that you can give to families and parents about what is the meaning of clinical research in the setting of an acute illness like acute flaccid myelitis? What is your, your, your advice and what is your main message for, for those families?

Dr. David Kimberlin: [00:34:20] Yeah, I think it's a great question. And, and, and, and, and really, you know, thinking about it from my, my own children, you know, and I understand sort of the protective aspects that's just intrinsic with being a parent. I think there's really two messages to provide. Number one, well, three, I guess. One is to acknowledge how scary it is for, for the parents at that particular moment in time.

[00:34:43] Also, you know, we know a lot about AFM, but we also have a whole lot left to learn. And, for instance, this particular study, this, you know, international study that we're, that we're all involved with, that's the best way to help your child. Because by contributing to that, you're tapping into the expertise of all these phenomenal speakers and the, the, the broader network that's a, that's part of this.

[00:35:11] So not only are you being taken care of at site A, you're, you know, hospital X, but you also are tapped into that much larger group. And that, that, that can only benefit that particular child. And then of course there's the more societal viewpoint as well, which is probably not going to be the primary focus of a parent at that particular moment in time.

[00:35:33] But, but by contributing to the study, but, but that altruistic approach may apply, may be, be attractive to some people. And it's a factual statement that by, you know, contributing to this, this group effort to understand AFM better you're going to make it easier for future parents who are in that emergency department or another emergency department around the world and facing the same kind of scary conversation.

[00:35:57] You're going to make it easier for that parent because we'll know so much more because of what you and your child are, are contributing to. So, you know, acknowledge where they're coming from. I think that's just being a good doctor and a, and a good human being. Recognize that, you know, there can be direct benefit simply by the, by the, for that particular child, by being involved, not from a therapeutic standpoint,

but from a knowledge standpoint of trying to help that child and the networking that, that, that sort of is, is behind the scenes.

[00:36:28] And then number three, that's how we make science and medicine better over the long run.

Dr. Carlos Pardo: [00:36:33] Thank you so much, David. That is a very, very excellent explanation for families. We really appreciate your involvement. One thing that actually is, is important about diagnostic criteria, and actually, in the audience, there are people from other countries. I just got an email from one colleague who is attending the symposium from Turkey. But I have our colleague, Jelte Helfferich. I apologize if I didn't pronounce your last name correctly. But Jelte has been actually a great collaborator in Europe, and he's based in Netherlands. So Jelte, give us your view about what is going on with the evaluation of AFM in European countries, the diagnostic criteria that you use.

[00:37:17] And, and give us an idea how these criteria may help to basically standardize the approach to all the patients around the world.

Dr. Jelte Helfferich: [00:37:28] Thank you, Carlos. And also thank you for having me here. I think up until now in Europe, the surveillance of AFM has been centered about enterovirus D68 and not so much about the clinical syndrome of acute flaccid myelitis.

[00:37:42] And I think the new criteria will very much help in spreading the recognition or improving the recognition of AFM in, in Europe. And I think it's important to spread these criteria amongst colleagues in, in Europe and England and UK has been involved in, in thiscriteria as well. And, we'll be working on improving the spread of this, these criteria and also improving the recognition of AFM because I believe in, in Europe, well there is some, some work to do still.

Dr. Carlos Pardo: [00:38:13] Thank you so much. There is one interesting topic is we have been very focused on acute flaccid myelitis to be closely linked to enterovirus D68. So, I'd like to ask Kevin and, and Matt Vogt, and later to Amy Rosenberg about how we are going to tackle understanding AFM from an etiological point of view and particularly trigger is, triggering factor for AFM.

[00:38:44] One of our colleagues in Turkey, Dr. Olcay Ünver, actually posted a question about... actually, they have a very good paper that I invite you to take a look. It was published in the European Journal of Pediatric Neurology, and this was the experience in Turkey with acute flaccid myelitis between 2016 and 2018.

[00:39:05] But one of his concerns is that there are other possible pathogens involved in the etiology of AFM and, and he mentioned the possibility of Epstein-Barr virus. But do you mind talking a little bit about other potential pathogens and, and also the importance of sample collection to investigate that? Kevin.

Dr. Kevin Messacar: [00:39:29] So I can start with just the broad statement that we've known that many different pathogens can cause this clinical syndrome of acute flaccid myelitis for a long time, most notoriously the family of enteroviruses, which includes poliovirus, enterovirus A71, and most recently enterovirus D68. But there are other pathogens too - West Nile virus, Japanese encephalitis virus, and other Coxsackieviruses and others that have also caused the same clinical presentation.

[00:39:59] So I think improving our diagnostics to try to get case-specific, pathogen-specific diagnostic tests, including the recent studies that have shown, even though pathogen may not be there, antibody in the CSF may be a way to link cases to that particular pathogen associated. And then secondly, Dr. Kociolek's comment of really beefing up our surveillance and knowing what's circulating at the same time as these cases.

[00:40:25] Because there may be cases in which we cannot associate it with a particular pathogen, but we know what's circulating at the time and what's then associated in a temporal epidemiologic standpoint. So I would say, I think we have good data that the predominant driver, at least in North America, in Europe, in even years since 2014 has been enterovirus D68.

[00:40:48] But we've also seen pockets of enterovirus 71. For instance, we had an outbreak in Colorado in 2018 of that particular pathogen. So I take the comment from the practitioner in Turkey to heart in that we do need to keep our eyes open. The epidemiology of this can shift over time. We need to have surveillance in place, and we need to be as prepared as we can for the next outbreak, whether it's due to enteroviruses or another pathogen.

Dr. Carlos Pardo: [00:41:14] Thank you, Kevin. Matthew, it's interesting that, as pediatric neurology, we always go to the CSF and we get frustrated that the CSF is negative for any detection of viruses. As an infectious disease specialist, give us your, your opinion when we are dealing in the emergency department with these patients.

[00:41:33] So what is the value of this sampling for understanding the etiologies? I mean, going from the nasal pharyngeal swabs to the CSF.

Dr. Matthew Vogt: [00:41:42] Well, and this definitely goes into what Kevin talked about earlier, how important it is to get these samples as early as you have AFM on your differential diagnosis. And, and what Kevin is talking about is the viral infection, which we understand from how, how the prodromal illness, you know, has progressed for typically many days before weakness sets in.

[00:42:02] The initial viral infection, if we're going to talk about enterovirus D68 as the example, you know, it happens many days before. And so these children have typically been having, you know, fever or upper respiratory symptoms for many days.

[00:42:16] And what we don't understand right now is where during that time, during that initial infection period, when does the virus cause pathogenesis in the spinal cord? Does it happen the same day that the virus starts replicating in the nose? Does the virus go to the spinal cord? Or is it later on? And so without knowing these, the answers to these questions, it's hard for us to know how significant it is that we very rarely detect the virus in the spinal fluid.

[00:42:46] And so by taking part in these studies that Dr. Kimberlin is organizing and then so many people on this call are part of, you know, we'll have a chance to start really aggressively collecting these samples, pairing them with prospectively banked clinical data, where we know a lot about this, a lot about the presentation of the patient and we can access their MRI data.

[00:43:09] And then we compare that with these biological samples - serum, spinal fluid, nose swabs, you know, stool or anal swabs. And that will allow us to, to, to better understand why it is that we oftentimes don't detect the virus. And I suspect it's because, as Kevin said, a lot of the initial viral replication in the nodes, for example, the longer we wait that dies down.

[00:43:32] And so even though there's still pathogenesis happening in the spinal cord maybe, you know, we miss that detection in the nose if we don't get it very early.

Dr. Carlos Pardo: [00:43:40] Thank you, Matt. That's very helpful. So I will ask, I would like to ask our colleague, Dr. Amy Rosenfeld, who is in Columbia New York. She is a virologist, and she works in the lab.

[00:43:54] And frequently, as clinicians, we forget very much what you do in the lab. That is actually the most critical part of research to understand pathogenesis. How sampling of these collections and then sampling of the nasal swabs, sampling of viruses, sampling of the spinal fluid. I mean, what is the advice, the recommendations that you give us for improving the detection of the virus and particularly to making sure that those samples arrive to research lab like yours that are focused on understanding pathogenesis?

Amy Rosenfeld, PhD: [00:44:30] So thank you. So I kind of almost slightly disagree with some of the stuff that Matt suggested. So we know, and Kevin has done shedding studies that EV-D68 is more like rhinovirus. You can detect it and then it rapidly decreases within three to four days of his shedding study, whereas polio went out much longer. And so there is a big difference in that. And the fact that if you go back retrospectively, people don't find polio in the CSF. It was really Bodian's brain that dictated whether or not polio is neurotropic or not.

[00:45:11] And we don't have that resource from autopsy children or autopsy bodies to the degree that they had for polio. So like Bodian looked at over 2000 people and made the brain and the spinal cord. And Matt's work is very elegant looking at one patient with AFM, who he sought RNA in the spinal cord.

[00:45:37] But that's not clear that the virus is replicating there or how it got there. So I think we have to be very careful about what we conclude and what we've learned in the past about these diseases and the fact that this is a virus that is more like a hybrid between rhino and polio. And so we need to take a step back with that.

[00:46:01] For sample collection and stuff, we do a lot of work, or we're starting a lot of, to do a lot of work with Ian Lipkin's lab here at Columbia. And we'd like to have samples as obviously as high quality as we possibly can. And we'd like temporal samples. So we want samples from the beginning of the disease when maybe the children just have respiratory all the way through the course of the disease and as many different types of samples, which I know I've spoken to Kevin about collecting, which are difficult because we are talking about a pediatric community.

[00:46:36] Parents don't always like children, their child's blood to be taken. So it makes a difference. Kids don't like needles. They don't like to sit still. So we are tuned to the fact that these are hard to draw, but we'd like them, you know, still. And we'd like them, you know, pretty much we'd like them to be easily transportable and transported as early as possible, but we understand that that's not necessarily the way to go.

[00:47:08] And with a lot of things that we can do today in the lab, we can recover a lot of genomic material and piece back the virus, which is not ideal, but we can also recover virus using a lot of different techniques that have been opened up recently. So we'd like, we'd like to know a lot more about not just the virus, but also the immunology and various other things.

[00:47:37] So like, what is, what is the composition of the pleocytosis? Not just what are the white cells, but, you know, what potential antibodies are there, or traces and various other things, would help us understand and help us develop a better animal model to test antiviral drugs, or to test vaccines or various... and even understand how it's trafficking from the respiratory tract into the CNS, because even still that is a huge open question.

[00:48:11] So whether or not from like Ken Tyler's work, it's respiratory trafficking from the neuron, or if it's more similar to polio and measles, which is another respiratory disease that enters the CNS and has a viremic stage that we're just missing. Because by the time the child presents with the AFM, the virus has probably already gone.

Dr. Carlos Pardo: [00:48:34] Thank you, Amy. Very helpful. Amy, how advanced is an animal model for AFM? I mean, I know that Ken Tyler has published his research that has been very good. But how advanced is an animal model for testing therapies? Is, is that something that you see is coming very soon or is it still a work in progress?

Amy Rosenfeld, PhD: [00:48:59] It's, from our perspective, it's still a work in progress. We appreciate Ken's work and the group, and the group in Utah's work using immune compromised or very young mice. Unfortunately those mice, the route of infection in those animals is not of physiological relevance. So we're in the process of actually establishing an animal model of mice that are slightly older that we can start off and look at the whole broad spectrum of EV-D68 or EV-D68 infection from the respiratory tract into the CNS.

[00:49:42] So it really all depends on what your focus is. And a lot of those animals, the virus actually doesn't replicate within the, what we think is the initial sites of infection of the respiratory tract. So they are limited.

Dr. Carlos Pardo: [00:49:58] Thank you, Amy. Good. So we are going to move back a little bit to the clinical setting for the diagnosis.

[00:50:07] And when we were discussing this criteria, one thing that we emphasized, and what's an important topic of discussion, is the clinical characteristics in the assessment of these patient populations suspected to have acute flaccid myelitis. Dr. Sarah Hopkins in Philadelphia actually is also, has been involved for several years in the assessment of these patients with the CDC.

[00:50:33] So Sarah, do you mind give, giving us your view, an overview about the initial clinical assessment that a clinician should have for any patient suspected with AFM and the clues that you have as a pediatric neurologist for clinicians around the world that are dealing with a suspected case of AFM.

Dr. Sarah Hopkins: [00:50:58] Sure, Carlos, I'm happy to. So, this is something we've been talking about a lot at CHOP recently because we've been building a, an AFM clinical pathway, and involving our emergency room physicians and lots of others in terms of being sure we have a good clinical case presentation and initial exam that's fairly simple and straightforward to use. So really important, of course, that you're considering it. And anyone who's had the acute onset of weakness with a flaccid component, regardless, as Dr. Greenberg said earlier, whether there are long track, long track signs or potentially some increased reflexes in some areas related to cord edema.

[00:51:41] Important to do a thorough neurologic exam. And I find one thing is, as everyone on this call really knows, you know, sometimes it's easier to do it from the top down and make sure you check everything off. Things that I find it's really important to remind the first, the frontline providers to check, are cranial nerves, specifically swallowing function.

[00:52:02] Things that can help us are knowing that AFM typically has a predilection for the cervical cord from about C2 to C5 and also the lower cord. So it's typically going to be your proximal, proximal muscles in your upper extremities more than your distal upper extremities. And also, it's almost always, almost always asymmetric.

[00:52:27] So it's usually going to be one extremity that's more than the others. Another thing it's important to remember to have people do is to really look for trouble with neck and trunk flection and extension.

Sometimes it's kind of noted as an aside in the notes that the patient's not really holding up their hand, holding up their head very well.

[00:52:48] That's really an important thing for AFM and really important to remember to check them for dysphasia and respiratory issues and, of course, cranial nerve abnormalities. The other thing we talk with a lot for front, with our frontline providers is what are the things that would make you suspect that a patient maybe doesn't actually have AFM?

[00:53:10] And of course, those are things like altered mental status, which doesn't typically occur in our AFM patients, unless it's related to the fever or ventilatory issues.

[00:53:21] We sometimes, we sometimes do see some kind of scattered sensory abnormalities in AFM, but it's atypical for us to see clear sensory, sensory levels. And it would also be unusual for AFM to progress very, very slowly as in over the course of weeks, rather than over the course of hours to days.

[00:53:42] We do typically, you know, try to get our samples as quickly as possible from the emergency room. Try to get imaging done as quickly, keeping in mind, as Dr. Rosenfeld said, that sometimes those tests, if they're done very early, can be negative. And also to keep in mind for our frontline providers, both at, both here and at other institutions, that we want to, we want to get those samples as early as we can.

[00:54:07] So if you're even, even suspecting that it could be AFM, we, we would rather have those samples and then decide later that it's not really necessary than to, to be kind of collecting them late.

Dr. Carlos Pardo: [00:54:20] Thank you, Sarah. One thing that is really important, particularly when we are evaluating these patients in the acute setting, is the decision for admitting the patient to the intensive care unit or the critical care management.

[00:54:34] And one of our colleagues, Dr. Sue Hong, who is in Chicago, has been also participant in the outlining the criteria for these decisions about intensive care management. Sue, do you mind giving us your view as an intensivist about what the clinician in the emergency department and the pediatrician needs to be prepared to when there are issues related with critical care?

[00:55:04] There are issues obviously about the respiratory management and the decision about intubation. Do you mind giving us your view of that conversation when you are attending in your intensive care unit and you are discussing an admission to your unit with a neurologist or with the emergency department specialist?

Dr. Sue Hong: [00:55:25] Sure. Can you hear me, Carlos?

Dr. Carlos Pardo: [00:55:28] Yeah.

Dr. Sue Hong: [00:55:30] Okay, perfect. I want to add to some of the discussion about early sample detection or collection of these patients, particularly when you're not sure of the diagnosis. And these kids will often be considered for receiving steroids and IVIG. And I think that obtaining samples prior to immunomodulatory therapy is pretty important, especially as we're learning more and more about AFM and in terms of being able to rule out NMO and MOG-related diseases.

[00:56:01] And these kids will often need sedation for LPs and for MRIs because they're young, they don't quite understand what's going on. And they're fearful of going into the scanner and they're fearful of needles.

And kids who are having neck weakness, proximal upper extremity weakness, bulbar weakness, dysphagia, drooling, issues like that, they are at high risk for respiratory failure.

[00:56:25] And so in considering whether these kids should be sedated and intubated for procedures, you treat them like any child with neuromuscular weakness and you would want to be able to monitor their saturations and CO2 levels carefully if you're able. Any kid who's going to be going into the scanner who you've chosen not to intubate but requires sedation, that there should absolutely be carefully monitored, because the progression to respiratory failure can occur rapidly and can occur while the child's in the scanner.

[00:56:54] And that could also include an inability to clear their airways and to clear oral secretions. Now when the child presents like this and doesn't, does not yet have respiratory weakness, I would advocate that anyone with risk factors, as I mentioned before, be admitted to an ICU for close neurologic monitoring, at least for the first 24 to 48 hours.

[00:57:14] If the child does not have those risk factors, I would advocate just an admission to an inpatient service so they can be watched closely while they're undergoing the diagnostic and therapeutic management. In the ICU, like any other kid with hypercarbic respiratory failure, you're going to be looking for their respiratory muscle strength, their ability to manage their oral secretions.

[00:57:35] And if you have a way to monitor CO2 levels, that can be helpful. And not providing supplemental oxygen without monitoring their CO2, I think is another thing to consider. If a kid does require intubation during the nadir of their weakness or as they're progressing in their weakness, once they're intubated, paying careful attention to aggressive airway clearance, suctioning, using meds or other augmentative therapies to keep secretions out of the airway is important for them to avoid atelectasis and other secretion retention. And then when it comes time to think about excavations, sometimes these kids are not extubatable. And if it's going to require a prolonged intubation, our group, the working group, tends to think that a tracheostomy should be considered sooner rather than later in order to facilitate early, early rehabilitation interventions.

[00:58:29] The other thing I want to mention is that autonomic instability can be a factor in AFM. And so that could be, manifest as bowel and bladder dysfunction. So paying close attention to voiding and potentially considering testing for post-void residuals, putting them on an aggressive bowel regimen to produce stools. And then also looking at their hemodynamics, their blood pressures and their heart rate.

[00:58:52] They can have pretty profound tachycardia, I might say is the most common thing. Some kids can have bradycardia, and also swings in their blood pressures. And so, having close monitoring of them, I think is another factor that may warrant admission to the ICU. I have managed some of these kids with bi-pap, and I have to say it's a bit challenging, and it also limits their ability to participate in rehabilitation. But that child that I did manage with bi-pap was able to successfully come off. I'd say that it may have, in the big picture, not been as ideal, again, because of his inability to get rehab related to his unsecured airway.

Dr. Carlos Pardo: [00:59:31] Thank you. So that's very helpful and a very comprehensive approach. Just a quick question about sedation and that always comes up in the emergency department when we are going to be doing an MRI, where we are going to do a spinal tap. Do you mind giving us your view about the use of sedation in that setting or even in the ICU?

Dr. Sue Hong: [00:59:54] It's ideal if you can choose a medication that does not suppress the respiratory drive, and within the paper, the example of dexmedetomidine is mentioned because of this benefit. There's no, you know, studies looking at whether these children tolerate versa or benzos or narcotics or ketamine, propofol, for example, better than other medications.

[01:00:17] So just looking at the, the physiologic effects that you expect from a drug, I think Precedex is a good one. Now the caveat to that is that it can precipitate bradycardia. And so if a child is having a profound bradycardic event, or a lot of hemodynamic instability, this may not be an ideal medication.

[01:00:34] Ketamine is also a drug that you could consider, but again, concerning the side effects of tachycardia, hypertension, and sialorrhea and bronchospasm in a child who may have respiratory failure. You have to, again, balance the risk benefit of each individual child when considering sedating medication.

Dr. Carlos Pardo: [01:00:50] Thank you, Sue. And I have a question for Sarah again and it's pain management. And I'd like to ask all the panelists to intervene here with the questions, if they have comments. But about pain, pain is an interesting manifestation in AFM. And pain is really a very stressful situation for not only for the patient, but for the family and people that are taking care of the patient.

[01:01:18] So, Sarah, give us your, your view about the pain management in the acute setting.

Dr. Sarah Hopkins: [01:01:23] So in, in our patients with AFM, we do often have a lot of pain, presumably at least to some extent, from the nerve root involvement. The, the medicine that we use most commonly on our inpatient service is actually probably Gabapentin.

[01:01:40] We find that we're able to increase the doses pretty, pretty quickly with minimizing, minimizing medication side effects, and also sometimes loading, giving a higher dose in the evening helps us get maybe a better quality sleep as well, which seems to help. I think the other thing that's really important also in these patients because they often do have the low neck and trunk tone is being aware of pain associated with GI issues and constipation, as, as well as bladder issues and really managing those aggressively to minimize that.

[01:02:13] But I would say in terms of medications for pain management, Gabapentin is probably the one that we use most frequently.

Dr. Carlos Pardo: [01:02:20] Thank you, Sarah. Any other comments from the panelists about pain management?

[01:02:26] If there is no comment about that, I'd like to ask Kevin, Kevin explore the potential use of some of the medications, antiviral medications, and other medications, in the treatment, at least during the past outbreaks. Kevin, do you like to give us the view of what you found with treatments and if, if there is anything that we should do in the next few months, if we encounter patients. And I will ask Matt also to give us an update about his approach published recently about the use of antibodies. Kevin?

Dr. Kevin Messacar: [01:03:05] So, first of all, I would say that there has been no standardized prospective studies of interventions as far as therapies for AFM. So the analysis we've done have been observational, meaning trying to learn from what was given clinically, which is not an ideal way to have objective data on what is truly effective versus what isn't.

[01:03:31] Our particular study is focused on the use of an off-label use of a medicine - fluoxetine - an antidepressant that has in vitro activity against enterovirus D68. And it was given to a number of children in 2016 for clinical care. And when we looked at the data observationally. There was not an impact in outcomes as far as we could tell, even when we tried to control for severity of disease. I would say that the most common treatments given to these patients are immunomodulatory treatments, meaning trying to calm down the immune response, inflammatory response that's going on in the spinal cord.

[01:04:08] I think IVIG or intravenous immunoglobulin is probably the most commonly administered medication when you look at the observational data. It has potential mechanisms of action via both immunomodulation and neutralizing antibody titers against some of the associated viruses. But when we did look at the data and kind of subanalyzed it, again, we couldn't see a difference between the groups that had gotten IVIG and the groups that hadn't.

[01:04:35] Again, those groups were not equal. Even when we tried to control for severity of illness, we could not see that or see a time to therapy difference. Other therapies, plasmapheresis and steroids have been attempted in specific cases. There are folks looking at the data for these therapies for particular indications. Ben Greenberg, if he's still on, might be able to chat about the use of, of steroids, particularly when there's either cord edema leading to compression and upper motor neuron signs, or in those cases where there's imaging findings outside of the gray matter and upper motor neuron signs in the lower extremities as he had talked about earlier.

[01:05:11] But I would say in general, we don't have a lot of data on these specific therapies, and we hope to do better moving forward. The one thing that we know that needs to be done meticulously was just, as you heard, is the supportive care and the support of the respiratory system, in particular when there's bulbar involvement in respiratory compromise.

[01:05:31] And those, those really are the essential strategies. There are therapies being developed [inaudible] on the call monoclonal antibodies towards enterovirus D68 are being developed, though not yet at the stage where they could be given to patients. So much more to do in this realm, and I would say our knowledge right now is incomplete.

Dr. Carlos Pardo: [01:05:50] Thank you, Kevin. Matt, give us an update about your antibody work.

Dr. Matthew Vogt: [01:05:55] Sure thing. So, you know, these monoclonal antibodies, much like a lot of the monoclonal antibodies that are now on the market for, for COVID are, you know, at least in animal models, theoretically active, but, you know, only in a sort of very narrow time window where they're being given.

[01:06:12] And so, if these do make it to market, I'll just proceed this by saying, they'll need to be given as early as possible, you know, when, when AFM is a thought. The antibodies currently that, that came out of the, of the lab I was part of when we isolated them, they're working their way towards phase one trials, but they have a few steps to go yet.

[01:06:33] And the steps, those steps are doing things like making sure these antibodies don't bind to human tissues. When we just look at them in a lab like using autopsy tissues before we put them in a human. And then also making sure that they're not toxic to rats when given in large amounts. These are very standard sorts of studies that must be done before we move into these phase one.

[01:06:53] So, you know, if everything goes very well, we are hopeful that within 2021 that, you know, there's the possibility of getting at least phase one safety trials under, underway and even completed. And the advantage of doing that is that I think we could say we could, even though, you know, as Kevin alluded to, it's very, very difficult to structure studies where we can test drugs or any sort of treatment really for efficacy in these still relatively rare diseases.

[01:07:21] When we think about numbers, we're talking about hundreds of kids over the last, at least in the United States, hundreds of kids, you know, over the last six, seven years, as opposed to something like COVID

where, you know, you're having, you know, hundreds of thousands and millions of infections, even within an individual country.

[01:07:37] So, so that will be the biggest challenge. Other good news though is it's not just us. So, I did a quick search on the NIH reporter, because I know there's been some small business awards given to some biotech companies. And so I can say, I know of at least four companies, whether with our antibodies or with other antibodies they're trying to develop, there are at least four different companies out there that are working towards a similar goal of trying to have anti-enterovirus-based therapeutics that may, with the, with the goal that they might actually be able to help in children with acute flaccid myelitis.

Dr. Carlos Pardo: [01:08:11] Thank you, Matt. I hope that we will have those tools, therapeutic tools, very soon. In the last few minutes, we are going to open the door to a discussion that we are not going to finish, because that will be the topic of discussion for next meeting is rehabilitation.

[01:08:31] So we have, obviously, a major concern that many of these patients are going to be left with significant neurological problems, disability. So I'd like to ask two of our panelists participating here, Joyce and Cristina, to give us a view about early rehabilitation. And I will start with Joyce is, Joyce, when we deal with patients in the emergency department that are admitted to the hospital, obviously the, the first question is they are experiencing an acute illness. And the main question that the family has is, okay, what we are going to do now, is there any magic medication? And the answer is there is no magic medication, but I always emphasize on rehabilitation.

[01:09:18] Joyce, what is your view? What is your recommendation for family and also for the clinicians about how to interact with the rehabilitation team in the hospital?

Dr. Joyce Oleszek: [01:09:28] Well, Carlos, we know that early rehabilitation is really the key for these children. You know, the majority of them, unfortunately, do have residual weakness, and the sooner we can get started on early initiation of, of therapies and preventative strategies to really help prevent things like contractures, pain like we talked about, orthopedic sequelae such as subluxation and... better we'll, we'll be in the long run.

Dr. Carlos Pardo: [01:10:00] Thank you, Joyce. Cristina, you are working at an institution that is caring for all of these patients, frequently many patients with acute flaccid myelitis. And what is the recommendation that you give or provide to the clinical group in the acute setting about the transfer to institutions like the rehabilitation hospital that will be taking a more dedicated effort for rehabilitation. So what are the criteria for saying, okay, this patient is ready for transfer? What is, what, what is your view and what are the recommendations?

Dr. Cristina Sadowsky: [01:10:36] Well, the first recommendation is medical stability. The second recommendation, the child needs to have a residual neurologic deficit, so he, he or she can qualify for an inpatient rehabilitation program. The specific recommendations for interventions that can be done in the acute side, acute phase of the hospitalization were already shown by Dr. Oleszek. Be in the, and they have to do with prevention and mobilization.

[01:11:12] We don't have a lot of long-term data on outcomes in these children because we have a small number of children that have been followed for a limited amount of time. But one thing that we know for sure, and there is data from other monophasic diseases, is that preserving or increasing muscle mass contributes to improvement in day-to-day function and preservation of other systems that are affected by paralysis, like for example, bone mass. So, my big push is medical stability, strengthening, preservation of, or increase of, muscle mass in the context of functionally adequate day-to-day exercises.

Dr. Carlos Pardo: [01:12:07] Thank you, Cristina. With this, basically we are coming to the end of our virtual forum. This is the first of other forums that we are going to have to discuss different issues related with acute flaccid myelitis management, rehabilitation. There are a lot of things to discuss in the future.

[01:12:28] We have other topics that are quite fascinating and important. In addition to rehabilitation, we have topics like nerve transfer treatments that are very interesting approach in the recovery of function of some limbs. And we will have those discussions in the next few months.

[01:12:46] The main message for the entire group and families, the participants in this symposium is, we should basically continue our effort for early diagnosis and very comprehensive management of patients with acute flaccid myelitis, to avoid difficult situations like long-term disability, long-term problems that actually are going to have a quite significant impact in quality of life.

[01:13:12] So we appreciate very much your involvement with the group. And, we invite our colleagues, the international sides to also get together. And we plan to have a meeting with the international collaborators in Europe, in Africa, in Asia, and South America to have a conversation about acute flaccid myelitis. So to the participants from those countries, they are very welcome, and we appreciate that they are able to come and participate in these discussions.

[01:13:43] And for the entire group, thank you very much. Remember, you may be able to get these educational activities and virtual symposium in the website of the Acute Flaccid Myelitis Working Group, and that's already active, and that's a very good source of information. So, again, thank you, all of you. And thank you to the panelists and thank you to all participants. And particularly thank you to the SRNA - GG, Rebecca, and all members of SRNA that have been, have been very collaborative and allow us to use many of the resources that they have and organize this meeting.

[01:14:22] Thank you so much and stay well and safe.