

# Acute Flaccid Myelitis (AFM)

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[00:00:00] **Chitra Krishnan:** It is my pleasure to introduce our next speaker, Dr. Leslie Benson. Dr. Benson is an Assistant Professor in the Department of Neurology and is also the Assistant Director of the Pediatric Neuroimmunology Program at Boston Children's Hospital. Thank you, Dr. Benson, for joining us and over to you.

[00:00:25] **Dr. Leslie Benson:** Thank you for the introduction. So, I'm pleased to be here today to talk about acute flaccid myelitis. We're going to try, I'm going to aim for 20 minutes on kind of an overview of AFM, hopefully highlighting some of the more recent advancements and then hopefully leave around 10 minutes for questions. I often talk, I can talk forever about AFM, usually for an hour at a time. So, I will do my best to keep plenty of time for questions and apologize if I fly past things. I'm happy to talk about it at the end.

[00:01:00] So, as Chitra said, I am Leslie Benson. I'm a neurologist at Boston Children's Hospital. For transparency, I always like to include my disclosures. They do have, I do work with a few organizations on AFM specifically, including the Massachusetts Department of Public Health as an AFM consultant. I'm a member of the CDC AFM task force and a PI on the AFM Natural History Study. My other disclosures are unrelated to this work, related to MS and clinical trials, mostly in the vaccine injury compensation program.

[00:01:39] So, let's start our discussion about AFM with just a little bit of background history. There, sudden cases of paralysis in the setting of infection goes way back, and polio used to be a very prominent disorder that is very much a vaccine success story with eradication of the disease in the United States. The last case was reported back in 1979. There have been no cases since then, and thus most medical professionals, including myself, never see a case of polio, going through training, although we learn about it, largely as the vaccine success that it is.

[00:02:26] There are polio unrelated, kind of rare cases of sudden paralysis in the setting of infection following eradication of polio. But really it wasn't until fall of 2012 when California surveillance and publications started to sort of raise some concerns about sudden paralysis cases. And then it was really in fall of 2014 when there was a sudden increase in cases that was clearly recognized. And it was in 2014 when people came together and coined the term AFM to name this condition that people were seeing but were calling different things at the time.

[00:03:11] And AFM just stands for acute, meaning fairly sudden onset, flaccid, meaning floppy, low tone, and myelitis means that there's inflammation in the spinal cord. Following the outbreak in, or the cluster in 2014 that was recognized, CDC has had ongoing surveillance and publishes this updated graph on a regular basis. And you see that there were additional clusters in the fall of 2016 and the fall of 2018. However, we didn't see a cluster case increase in the fall of 2020. And that is pretty clearly associated with the increased infectious precautions around the COVID-19 pandemic. And so, when, and how much, what the future holds is, I think, an area of uncertainty, but still ongoing concern.

[00:04:10] So, with that background history, I want to talk a little bit about what the patients demonstrate or experience through the course of AFM. And I think that this very succinct graphic from Dr. Messacar's paper, back in 2016, is a nice way to think about it. Basically, looking towards the left, the patients have a prodromal illness, usually within about 7 days before onset of neurologic symptoms, with fever and most often some sort of respiratory illness, some upper respiratory infection, but can be a GI infection, doesn't have to have fever.

[00:04:53] And sometimes it's maybe a bit more of a prominent infection than a typical, but nothing crazy, out of the norm, or with clear neurologic problems, typically with that prodromal piece. Then patients can have a recurrence of their fever or worsening of their fever or no fever. And sometimes headaches, stiff neck, often times neck, back, limb pain that occurs just as weakness or just before weakness and low tone sort of onset. And that weakness and low tone progress and usually reach their worst within hours to days of onset.

[00:05:39] The classic and kind of most predominant is usually limb weakness, although they can have, patients can have cranial nerve palsies, which can include things like difficulty moving their eyes, difficulty moving their face, and difficulty moving their swallowing muscles. And even sometimes, some sensory changes beyond the pain and on occasion altered mental status. After that, kind of they hit their worst, then they enter the phase that's called the convalescent phase. Which is really the recovery and to the new normal that occurs over months to years following the acute period of illness.

[00:06:27] There really is a wide spectrum of disease in my experience. So, I've seen patients who present with just a minor limp, really subtle proximal one leg weakness, for example. Others who have much more clear weakness. The classic is, and most common, is particular proximal arm weakness, most often asymmetric arm weakness. And then, on the most severe end of the spectrum, there have been reports of such severe paralysis and respiratory failure leading to death when the respirations were not supported.

[00:07:08] So, I want to also review kind of how do we make a diagnosis of AFM, knowing that those are the classic symptoms, how do we decide if something is AFM or something else? And point out that there is no diagnostic biomarker. So, there's no one test that a doctor can send off and say this is definitely AFM or this definitely isn't. We currently use clinical constellation of symptoms. The CDC has always, has consistently put out and updated a case definition which is really intended to guide surveillance and epidemiologic observations and study. It was never intended to make a clinical diagnosis but was helpful in thinking about what did AFM look like and what was typical.

[00:08:03] There's been a need for clinical and research criteria and that's one of our big updates this year is the AFM working group came together and over a series of calls and time, led by the group with Dr. Pardo at Hopkins, who kindly allowed us to share these slides, came up with a proposed set of diagnostic criteria based off expert consensus.

[00:08:30] And what I'm showing you here is a table that walks through what aspects do we think about, what aspects of presentation contribute to the diagnosis and the diagnostic certainty. And so, there are

pieces of the history, pieces of the exam, the MRI components and spinal fluid components that get taken into consideration. And then using those can classify the level of certainty of the diagnosis for research purposes. But likely also for clinical purposes, hopefully, in the long-term. These will need to be validated and have ongoing considerations. But I think it's a big, it's an exciting advance in AFM.

[00:09:25] So, going off of that, let's think about the testing. How do we come to a diagnosis of AFM? And really the most important test that gets done, there's a lot of tests, but the most important one is an MRI of the spine. And it should be the entire spine and we typically recommend with and without contrast because that gives us clues as well. I put MRI brain as a tiny thing down below because that really shouldn't be the emphasis. It's important to rule out other mimicking conditions and such, but it's really not where the majority of the imaging effort should go, in my opinion, or be the priority because that can make the spine imaging hard for the patients to tolerate and for a very long scan.

[00:10:10] In order to help you see what abnormal imaging looks like, I want to first walk you through what a normal MRI looks like for comparison. So, on the right, you see a, basically what we call a sagittal section where it's kind of dividing and looking at a picture as if the patient were divided right down the middle. And at the top is the bottom of the brain and then the spinal cord is the long gray structure that extends down within the protection of the vertebral column and that spinal fluid.

[00:10:46] And I want you to note that that whole, long gray cord is very, is the same shade of gray all the way throughout. Similarly, the middle picture is a cross section, what we call axial cut through the spinal cord. And it's that little oval structure in the middle circle that is the spinal cord.

[00:11:08] And again, it's pretty kind of the same shade of gray all throughout. Even though we know that within that spinal cord there is white matter on the outside of the spinal cord and gray matter in the middle. That gray matter is where the nerve cells live, and the white matter is where the wires that are covered in myelin travel through the spinal cord.

[00:11:34] And so, this is an example of what a patient with AFM looked like. So, you can see, as opposed to the last picture, this spinal cord on the left now is not the same shade of gray all the way up and down. Here by the top arrow and the bottom arrow, you see significant brighter signal in the middle of the cord, not at the edges, but in the middle, which goes along with this cross-sectional little image where you see this bright, whiter "H" kind of shape.

[00:12:08] And that is showing you that it's the gray matter, that "H" is the gray matter, middle portion of the spinal cord that is sick, that is abnormal in this patient. It doesn't always show a full "H," sometimes it's mostly in the front. Sometimes it's one side more than the other. But these are some of the different patterns we can see.

[00:12:34] The reason we give contrast, that's the contrast dye that goes into the IV, is to see if there is leakiness of the blood vessels and that that contrast can leak out into, and a classic pattern with AFM is that we see anterior nerve root enhancement. So that can be seen higher up in the spinal cord as well. But often it's easiest to see in this bottom lumbar part of the spinal cord where you see that these are much brighter than the back.

[00:13:05] And on the cross section, you can really see that these nerve roots that come off the bottom of the spinal cord are bright in the front ones and dark in the back ones. And that's a classic pattern that we look for. It can be a diagnostic clue. In addition to MRI, we do lots of other tests and we try to do those tests as

early as possible to increase the chance of catching a virus or an infectious trigger culprit early on because if it takes time, the body can clear that infection after it's done its damage and we can't always get, detect it in the fluids.

[00:13:46] We check the nose swabs, the mouth swabs, blood, stool, and spinal fluids. CSF is cerebrospinal fluid. And we send those samples both to our state lab, they get sent off to the CDC for testing for reported patients, as well as to our hospital labs for clinical testing. And really the point of those swabs are to look for enterovirus D68 and other viruses that can cause sudden paralysis. The other thing we're doing is we're sending tests to look for things that can mimic AFM, particularly MOG antibodies, which you'll hear a lot about in this symposium, as well.

[00:14:29] Okay, so, I want to talk a little bit about the cause and what we know about the cause. There's a lot of good science out there, but, sorry, I want, we'll go through a couple studies. And just to say that, since 2014, we've learned a ton from the epidemiologic studies, mice, viral gene studies, neurons, and now human spinal fluid studies.

[00:14:52] And so, this is a study that was done after the 2014 outbreak, and really the point is to show that enterovirus D68, in this lower graph, hit and caused a lot of respiratory symptoms right before they saw a peak in AFM, back in 2014. It's sort of one of the first clues that these two things, AFM and EV-D68, were likely linked. Then Dr. Tyler in Colorado created the first acute flaccid myelitis mouse model, and we've learned a lot from, sorry, it's jumping around, from that model as well.

[00:15:32] So, basically, just like the flu, when you get your shot, it has multiple strains of virus that are expected to circulate. There are different strains of enterovirus D68 that were isolated in 2014. And they took five of those strains, and they found that four of those strains, when given to mice, could cause paralysis. And they found that depending on the age of the mouse, the younger mice were more likely to develop the paralysis, and they also tried giving them the virus in different ways. And they found that if they injected it into the muscle as opposed to the stomach or putting it in the nose or the brain, it actually was more likely to cause an AFM-type picture which is really interesting.

[00:16:13] And then they also looked at the mice that had had basically AFM and found that they had lost motor neurons, that nerve that controls the muscles from the spinal cord, that they had a detectable virus, virus particles, and virus genes in the spinal cord. And then if they took a mouse who had AFM, and they took their, basically their blood or bits of their blood and gave it to a mouse before they induced AFM, they could protect the next mouse from AFM, all very convincing that EV-D68 caused AFM in mice.

[00:16:50] But mice aren't humans, so we need some more data. And subsequently there's been some interesting in the lab experiments on neurons and viral genomes and such. But I think one of the most important things and most recent things is that these two groups fairly concurrently reported that you can detect antibodies to enterovirus in the spinal fluid of patients who have had AFM and not in other conditions. And so, I think these studies were really a nice turning point in feeling like this disease was less mysterious and more clearly associated with EV-D68 in humans.

[00:17:38] The other recent exciting advancement is that a group has been able to develop, identify and develop a new monoclonal antibody therapy, we call it. So, basically, this is an antibody, like your body is expected to make to an infection, but a specific antibody that attaches to and neutralizes, meaning makes the virus not able to cause problems. And this is an antibody specific to enterovirus D68. And it has been shown in the

mouse model to be able to prevent or reduce the severity of EV-D68 in that mouse model.

[00:18:25] The next phases are going to be looking at the safety of this in humans. It's an exciting, it has exciting implications for both the ability for a vaccine to prevent the disease, if that is appropriate, as well as potentially a treatment. There's lots of challenges to treatment, but it's an exciting development. I think, in the interest of time, I'm going to keep this slide short and talk just quickly about treatment, but not on a granular level. Please send me questions if you have specific ones.

[00:19:01] But, basically, I think about treatment of AFM in different buckets. One bucket is acute treatment. So, you're sick in the hospital. You just had this illness. What can I do to reduce inflammation, to ideally address the virus that we know is causing the problems and protect the neurons? Next is the symptomatic and supportive therapy. How do I keep the patient comfortable and stable in both the acute and long-term situation?

[00:19:32] And that sort of morphs into chronic rehabilitation, which is the things that can be done to optimize recovery and function long-term. And surgical interventions certainly kind of fit into the second and third bucket, but are, I think about them somewhat separately, in terms of their role and who pursues them. There have been some recent publications now about the results of nerve transfers, which has been a big topic of discussion in AFM. These are a procedure to basically taking a stronger nerve and connecting it to a weaker nerve and allowing regrowth to improve function of that receiving nerve. I think there's still a lot to learn but some promising results there and typically a time sensitive consideration.

[00:20:33] Other things that come up are things like muscle transfers or tendon transfers which are less time sensitive and can be considered to optimize function longer term. And then there are obvious things like intervention for scoliosis, leg length discrepancies, other roles for an orthopedist, for example, in AFM in the long-term.

[00:20:59] And then the last slide I'm going to talk through is prognosis. So, we know from early epidemiologic studies that the response to acute treatment, as well as the degree of recovery is not as good as we would like it to be. And the majority of patients have long-term consequences from AFM. Here is a table just sort of listing some of the many, not fully inclusive, but some of the many things that we think about and watch for long-term in AFM patients. And I'll just highlight some of the most frequent being things like subluxations of joints or dislocations of joints, particularly the shoulder can be quite weak, with leg involvement, discrepancies with the weaker leg being shorter and not growing as well as a stronger leg, for example.

[00:21:55] Scoliosis and muscle contractures can still happen, even with long-term low tone or some patients who have a mix of high and low tone. And then we do think about bone health, as well because with lower muscle bulk and tone not pulling on those bones, they don't get all the input that their healthy bones are supposed to get and they can get quite thin. We've seen unfortunately a number of fractures that involved limbs related to that low bone density, as well.

[00:22:34] In the interest of allowing questions, I am going to leave you on this last slide and not run through everything, but just open the floor for questions. Chitra, if you want to tell me if you want me to, if I need to stop sharing in order to do that.

[00:22:52] **Chitra Krishnan:** Hi, that was so fantastic. Thank you for going into such wonderful detail explaining the imaging and actually spending time on it. It's invaluable the way you sort of explained things. I know we have about five or six minutes. One of my questions, as you were giving this talk, was really about long-term,

follow-up studies, like since the first, when we called it AFM in 2012 to now, what do you, are there studies going on? What are some of these long-term effects that we are seeing in your practice with people coming back as you're following them?

[00:23:26] **Dr. Leslie Benson:** That's a great question. And I don't think we have as much of a long-term follow-up formal study as we would love to have. The NIH Natural History Study was a big advance to have set up. Unfortunately, it sort of got rolling right as the pandemic hit. And so, we have yet to learn a lot from it. And that study will follow patients for the first year. And so, we'll learn a lot from that first year. But I think we still, there's still a need for formal prospective, meaning following the patient over time, studies after that because it's still early. 2014 to 2021 is not that long.

[00:24:03] And so, while patients have recovered and are learning functional gains and dealing with the consequences of their AFM, it's been less than a decade even for the earliest patients. And so, I think there's still a lot of unknowns about longer term that we need to explore.

[00:24:25] **Chitra Krishnan:** Thank you. And then, we've always just talked about these peaks for AFM and, of course, with the pandemic, things have been different. Are you seeing children with AFM in your practice now? What do you think? What do you anticipate?

[00:24:43] **Dr. Leslie Benson:** I'm following patients who had AFM in the past. I have not seen new AFM, classic AFM, EV-D68 cases in my practice since 2018. Maybe not fully 100 percent, but not like we did. It's been very few and far between.

[00:25:07] **Chitra Krishnan:** And a question we get often, people will ask us is about the differentiation between transverse myelitis and acute flaccid myelitis. And while you walked through the diagnostic criteria beautifully and the AFM working group has really worked so hard in coming up with a consensus diagnostic algorithm, a lot of people will hear, will say, "I was diagnosed with TM, but as I read and hear about AFM, I really think I'm AFM, in retrospect." What are your thoughts on that?

[00:25:41] **Dr. Leslie Benson:** I think it gets into semantics and possibilities, and it's a hard question to answer. I certainly look back at some patients, and it's like, "Man, you really seem to have had a big hit on your motor neuron. I wonder if you had more of a viral myelitis, rather than an autoimmune myelitis." But there's so much unknown about TM anyway. We don't really understand and not every TM looks the same. Some TMs respond beautifully to inflammatory treatments, and some don't. Why? I don't, we don't know, and we don't have great predictors.

[00:26:15] So, I think that's a challenge in differentiating the two, as well as the field, in general, but I do kind of think of them as an infectious versus an inflammatory, distinguishing the two in terms of their primary pathology.

[00:26:35] **Chitra Krishnan:** That's very helpful. And sort of looking at the future and looking at your slide on future directions, where do you think we are with sort of vaccines and therapeutics outside of what we use now?

[00:26:53] **Dr. Leslie Benson:** That's a good question. I think that the AFM is still rare enough that I don't think that a vaccine is in the near future as something that people, and COVID and vaccine acceptance and such, it's so political. I would say I don't think we're anywhere near a vaccine for AFM now, but if it did become a more frequent problem, I think that there would be ways to quickly move towards a vaccine. That I'm optimistic about.

[00:27:18] Treatments, I'm excited about the monoclonal antibody, but whether we can get it where it needs to be and give it fast enough, is still something, and give it safely, are things that we have to work through, but I think there's been significant advances and promises there. I didn't see anything else that I'm particularly ready to jump on, but certainly there's some other things in terms of viral, antivirals and things that may come down the pipeline.

[00:27:46] **Chitra Krishnan:** Fantastic. Thank you so much, Dr. Benson. This was a fantastic talk. I really appreciate you taking the time.