What is Acute Disseminated Encephalomyelitis (ADEM)?

You can listen to the audio of this talk at: https://youtu.be/TWX4j0tNwSY

Dr. M. Mateo Paz Soldán: [00:00:00] Thanks, Dr. Sweeney for the introduction. So, I'm going to talk about, ADEM, as was pointed out. So, ADEM, it's an acronym, and we'll just go through each of the letters, and say a little bit about what that means, and what that, tells us about the disorder. So, the A stands for acute. And in this context, we're talking about the timeframe from which symptoms are first noticed until they reach their most severe point. And for ADEM, it's really worsening over a number of hours to days. You know, if it happens within seconds or minutes, that's a different sort of timeframe not consistent with ADEM. If it happens over weeks, or months, or years that symptoms are changing, then that's also not consistent. So we're looking for some neurologic symptoms that are evolving over hours to days.

[00:00:56] The, D refers to disseminated, and what that means is that there's many parts of the central nervous system that are involved. There are some situations where ADEM can also involve the peripheral nervous system, but largely, and almost always it's a disease of the central nervous system. And so that means different parts of the brain, different parts of the spinal cord, the optic nerves can also be involved. And so there's symptoms that can come from any one of those areas of the central nervous system.

[00:01:32] The E refers to encephalopathy, and that tells us that the brain is involved with this process. And it's actually a requirement for the diagnosis, which I'll talk about a little bit more later. So, encephalopathy, inflammation in the brain, it definitely causes, neurologic symptoms, that we associate with this disorder. And then the myelitis, refers to inflammation in the spinal cord. There are lots of important pathways in the spinal cord, and symptoms can arise from involvement of the spinal cord as well. So that's the acronym, acute disseminated encephalomyelitis, and it's telling us the timeframe, it's telling us how widespread it is, and it's referring to some important symptoms that we typically see, especially encephalopathy.

[00:02:24] A little bit about the epidemiology. So as you might expect from the title of the conference we're having today, this is a rare disorder. It's much more common in children, than in adults, but it's not occurring very often. So, different studies might find different number of children who develop ADEM each year, but somewhere in the point two to point four per 100,000 children range. So, qualifies as a rare disorder. Most of the time, children who develop this are between the ages of three to seven, but it can happen at most any age. There's also ADEM that can occur in adults. It's much more rare in adults than in children, and so we don't actually even have estimates about how common it is because of how rare we do see it in adults.

[00:03:24] Typically, it happens after there's been an infection or an illness of some sort. In children, a febrile illness or a viral illness, is most common. And in the studies that have been done over many years, somewhere around 75 percent of children who develop ADEM, it can be identified that they had some sort of illness preceding that, usually a viral upper-respiratory syndrome. In adults, the

finding of a preceding illness is less consistent, but similar numbers. It can be identified in perhaps 50 to 75 percent of adults who had developed ADEM, that there was a preceding illness. And so that's an important piece of historical information when we're first evaluating children or adults suspected to have ADEM is to ask about how they were feeling over the few weeks preceding that.

[00:04:25] So as I mentioned, the E stands for encephalopathy. This is an important aspect. And in years past, there was some disagreement about whether encephalopathy was an absolute requirement. But there's been international experts who have sat down over the years, published papers, you know, most recently, back in 2013, really, clarifying that encephalopathy is an important part of making the diagnosis of ADEM. And the reason is that we can see inflammation in the brain that involves multiple different parts that doesn't bring encephalopathy, and we should think carefully about what that diagnosis is, because typically it's not ADEM, and doesn't have the features that I'll talk about a little bit later, most importantly, the time course that we typically see. So, in the current diagnostic criteria for pediatric onset ADEM, encephalopathy is necessary.

[00:05:31] So what does encephalopathy mean in terms of symptoms? So it can manifest in a number of different ways; inflammation in the brain, can cause a decreased level of alertness, and so that's drowsy, or sleepy, difficult to wake up the child. It can also result in some behavioral changes, which might manifest in different ways depending on the age of the person who develops ADEM. In children, it might just be irritability or more tantrums. But either some decreased level of alertness or some change in behavior is a necessary part in the symptoms to think about the diagnosis of ADEM.

[00:06:15] It's also multifocal. So I mentioned a little bit earlier that many parts of the central nervous system can be involved; so, spinal cord, different parts of the brain, it can involve both the white matter and the gray matter, and the symptoms that come along with that really reflect the part of the brain that's affected. If it's affecting the optic nerves, there would be vision changes, if it's affecting the spinal cord, there could be weakness, there could be sensory changes, could be changes in bladder function or bowel function. And as I was already mentioning, different parts of the brain might lead to some behavioral changes or some decreased alertness.

[00:06:59] The other thing that's important is that it's typically a monophasic disease. So the clinical course, acute onset, meaning worsening symptoms over hours to days, and usually the maximum severity of the deficits is reached within the first week. It doesn't often continue to worsen beyond that but can be quite severe by the end of a week. It, usually has the severe phase, doesn't last more than a month or so, can last longer than that occasionally, but especially not longer than three months because then we start to fall out of the timeframe that is consistent with ADEM, and we need to think carefully about other diagnoses. So, worsening symptoms over hours to days, hitting maximum severity within a week, and staying in the most severe phase for about a month or so.

[00:08:00] Patients typically recover quite extensively, and often completely, especially when ADEM is seen in children. There are some different versions of ADEM which I won't mention which are more likely to leave permanent neurologic dysfunction, but sort of standard, run-of-the-mill ADEM can be quite severe at its most severe neurologic deficits, but typically recovers completely with appropriate treatment, which I'll mention later. Occasionally, it can be what's been termed

multiphasic, so a second attack can happen after some timeframe beyond the first attack. It has to be at least three months away from that first attack, otherwise we just consider it some waxing and waning of symptoms, some fluctuating of symptoms that's related to the monophasic episode.

[00:08:56] If it's more than three months since the first episode, then we would term it multiphasic ADEM, but that second episode also has to meet all of the criteria, diagnostic criteria, for ADEM, and in particular, encephalopathy as I mentioned is an important component. Sometimes we make mistakes about calling a second episode ADEM because there was a first episode that was definitely meeting criteria, but the second episode doesn't have encephalopathy, and then we need to think carefully about what that is. So in children, if there's a second episode, it usually happens within the first several years. I'll say it more specifically, if there's more than two attacks, that's not consistent with the diagnosis of ADEM, and then we need to think about what the diagnosis is, then we're talking about a chronic, inflammatory disease that's at risk for recurrent attacks, and then that changes our idea about diagnosis, and our idea about treatment.

[00:09:59] Things that it could be if there's a first episode that clearly meets diagnostic criteria for ADEM, but then there's subsequent episodes more than, you know, two or more, or the future episodes don't have encephalopathy, then that can be multiple sclerosis, it can be neuromyelitis optica, MOG associated demyelinating disease, and various other things that we think about. And I'll say specifically that for multiple sclerosis, in children in particular, the first episode can absolutely meet the diagnostic criteria for ADEM, but it's the occurrence of additional episodes in the future, more than two, don't have encephalopathy, that really tells us that that's a diagnosis of multiple sclerosis and not just more and more episodes of ADEM.

[00:10:53] So, I'll talk a little bit about how we do make the diagnosis. MRI is a very important tool, and as I said a few times already, multiple parts of the brain can be involved. That's both the white matter, and here's a picture of what that would look like on an MRI. The lesions tend to be on the larger side, and so that's, you know, one or two centimeters, or even larger. They tend to have poorly demarcated edges. So that means they look a bit fuzzy when we look at the MRI, or a little fluffy, been called various things, but that's in distinction to some of the other disorders that I mentioned. Like multiple sclerosis, for example, which tends to have more distinct edges to those bright spots in the brain MRI, and ADEM looks a little bit more fuzzy.

[00:11:44] Also, there can be involvement of the gray matter. The deep gray matter structures, the thalamus, for example, can definitely be involved with ADEM and can contribute to some of the encephalopathy that we see. I mentioned a little bit earlier optic neuritis can happen in ADEM, transverse myelitis, so that's inflammation in the optic nerves or inflammation in the spinal cord. It's also important to have spinal fluid studies. Not because we're looking for specific things that tell us this is a diagnosis of ADEM, but because we want to look for other reasons that there can be inflammation in the brain and some of those bright areas that we see on the MRI. And most importantly, we're worried about infections, and so, typically we'll do spinal fluid tests and look for a whole wide variety of infections that can cause different patches of inflammation in the brain.

[00:12:40] If it's ADEM, sometimes the spinal fluid is completely normal. That doesn't mean it's not the right diagnosis, it just means that there's not as much inflammation that we can see it in the

spinal fluid. But more often than not, we do see evidence of inflammation: an elevated number of white blood cells, or an elevated protein, for example. We also will tend to some serum tests, and that's to look mostly for neurologic antibodies that would be markers of some of these other diseases I mentioned earlier, like neuromyelitis optica with the aquaporin-4 antibody.

[00:13:19] And then the pathology, we don't need biopsy to make this diagnosis, and we certainly would try to avoid that. If we think it's ADEM, we wouldn't biopsy, but sometimes there's that lack of clarity, and biopsy, has been done in the past. And if you look at that tissue under the microscope, there's a number of features that are clearly present. So, swelling in the brain, there's lots of movement of different types of white blood cells into the brain, and it has this interesting pattern, where it tends to cluster around the small veins in the brain, or what's called the perivenous area.

[00:13:56] And here's a depiction under the microscope, where we can see some of the demyelination. So, here are these little dots, or some of those small veins, and this blue is stained for myelin, and you can see there's little patches around the veins where that myelin has been lost. And that's sort of a patchy pattern, and really is the reason that on the MRI it tends to look a little bit fuzzy or fluffy, because the underlying pathology at the microscopic level is a patchy pathology. And that's different from, say, multiple sclerosis, which has much more of a uniform and confluent loss of myelin.

[00:14:39] So now I'll mention a little bit about treatment. The mainstay is steroids, and there's a couple of other acute treatments that I'll mention in a minute, but steroids, really are the thing we think of first for a couple of reasons. It's simple to give and get started while we're still in the process of trying to make sure we're not missing a different diagnosis, like a brain infection. And we can also give steroids at the same time that we're giving medicines to treat possible infections, so antiviral medicines, antibacterial medicines. Usually we give those while we're sorting through what the diagnosis is at the same time that we're giving steroids. Usually it's a five-day course, and we want to see that really within the first three or four days that there's some clear evidence that symptoms are improving. And if they're not improving, then we move onto a second acute therapy. So, steroids we start with almost always, and if there is improvement, then we typically will have some prolonged lower dose of oral steroids to help consolidate the improvement and limit the chance that there might be a worsening before a complete recovery.

[00:15:57] So, another key therapy, IVIG. This is a blood donor product, so pooled immunoglobulins from different donors are given to, the person with ADEM. That's more common in children to use IVIG. The other acute treatment is plasma exchange. That's sort of like a dialysis type of procedure where the blood is removed, the plasma is exchanged with an artificial plasma, and then given back to the individual. The important thing about these other therapies is if one doesn't work as our second therapy, then we try the other one, because we really want to see that there's improvement.

[00:16:35] So that's all I was going to talk about. So I'll introduce our next speaker, Dr. Stacey Clardy, who is an Associate Professor here at the University of Utah and one of my colleagues here, and she's going to talk about transverse myelitis.