Acute Disseminated Encephalomyelitis (ADEM)

You can view this presentation at: youtu.be/uxFicEFUmk8

[00:00:00] **Krissy Dilger:** I'm pleased to introduce Dr. Cynthia Wang. She is an assistant professor in the Departments of Pediatrics and Neurology and Neurotherapeutics at UT Southwestern Medical Center, and a pediatric neurologist at Children's Health. And Dr. Wang is also a former James T. Lubin Fellow of SRNA. And I will give it over to you Dr. Wang.

[00:00:30] **Dr. Cynthia Wang**: Okay, great. Thank you very much, Krissy, for the introduction, and thank you to the Siegel Rare Neuroimmune Association for inviting me. It's always great to be a part of this, even if it's virtually. Hopefully, that allows a lot of people who may not have been able to attend a physical event to still participate and ask questions. So, yeah, I will be talking about acute disseminated encephalomyelitis today. I'll try to make my slide portion of the talk relatively brief, so that there's still going to be some time at the end, hopefully, for some questions and answers.

[00:01:03] And yeah, feel free to type your messages and Krissy will direct me to those as we wrap up the more formal part of my talk. So, my disclosures is I was, yeah, very, very lucky to have been supported by the SRNA to pursue understanding these types of conditions and doing some research on ADEM, that I'll present on Sunday.

[00:01:33] And because so little is known about these conditions, I will be discussing mostly off-label use of therapies. So, we'll start with a case presentation. This is a 5-year-old boy that presented after a few weeks of some symptoms, including a worsening headache, some right eye blurry vision, some vomiting. He initially went to a local ER where he did test positive for COVID, so this is a case that happened in the past year.

[00:02:02] His symptoms were attributed to this illness, and he was discharged home with parents advised just to kind of do supportive care. He unfortunately returned because his headache did not get better. He had another positive COVID test. His neurological exam was not that exciting per report, though he was quite irritable, and this seemed to be out of proportion for the illness symptoms. And sometimes he would be kind of sleepy as well. So, at this point, his physicians ordered some imaging of his brain and his spinal cord, which showed the following.

[00:02:41] So, here on the far left, you're seeing the, what's called a T2-FLAIR sequence that really brings out abnormalities on MRI brain. And all the areas that aren't the more dark gray is areas of swelling or inflammation in the brain. Here we see when we inject dye in the patient to see which areas seem to be the most inflamed, that there's actually some penetration of the blood-brain barrier. It's in those areas that we see the most abnormal signal, and his spinal cord is also affected, as you see in these images. I'm sorry. Let me actually move this over a little bit.

[00:03:26] With a pretty long lesion and again in the most affected areas, there is dye that leaves the blood vessels and goes into the tissue of the spinal cord. And I share that case because I think this child has many of the features that we consider consistent with acute disseminated encephalomyelitis. His symptoms came on relatively suddenly over usually days to a week or so. That he has widespread inflammation. You saw those lesions in both his brain and his spinal cord. And our best guess of what's causing that is some sort of overreaction or abnormal response of the immune system.

[00:04:12] All this inflammation can lead to either swelling of the myelin, that insulating coating of the nerves that helps signals be conducted. And in cases where that injury goes on too long, maybe some loss of myelin or demyelination. When there are so many parts of the nervous system that are inflamed, there is often this term that we use called encephalopathy, but really just means the child is behaving normally, maybe tired, maybe irritable, but just something seems to be wrong with how they are responding to their environment. So, as a pediatric neurologist, I'm very invested with this condition because it affects children preferentially.

[00:04:59] And the average age of onset is. This patient is pretty typical. It's usually that early grade school age. A few cases per million children occur each year. Seems to be that males are slightly more affected than female children, and it's more common probably in the places and in the seasons in which we transmit more infections, because in the majority of time there's a history of some sort of illness in the weeks preceding this presentation of neurological symptoms.
[00:05:38] And then, because I think we use a lot of terms that sometimes we don't do a good enough job in defining, I thought I would just put some of this out there. Encephalopathy, again, is a really key characteristic of this condition, where there's brain dysfunction changing how somebody may be perceiving the environment, thinking, and processing that information. To go a little bit more in-depth, or rather, encephalopathy just means that there's some sort of dysfunction, which we can tell from how the person behaves and looks on their exams.

[00:06:14] Sometimes by looking at their brain waves to see if there's abnormalities. ADEM usually implies even going further than that, in which there is actually inflammation as we can tell from neuroimaging, spinal fluid studies, and in rare cases, when we take a look at the tissue under the microscope. In some cases, the immune system can be doing what it's tasked to do, which is to fight off infection. If you have a bacterial viral meningitis or meningoencephalitis, we do want the immune system to be there and doing what it's supposed to, to keep the person healthy.

[00:06:46] But in cases of autoimmune encephalitis, like ADEM, when the immune system is targeting perhaps a cancer, which is called paraneoplastic encephalitis, we think that the immune system's response is sort of out of proportion to the... what's going on in the body, so that the inflammation is kind of preceding unchecked. The clinical presentation, again, is things that evolve over a couple of weeks. In the beginning, it can be also simultaneously associated with symptoms of fever, headache, nausea. And then, it really just depends where the inflammation occurs in terms of what the symptoms are and how severe they are.

[00:07:30] Confusion, sleepiness are very common symptoms, but it can progress to being in an almost comatose state if there's enough inflammation in the brain. If it affects the spinal cord, there may be weakness

or numbness or bowel and bladder dysfunction. If the inflammation affects the optic nerve, it can lead to blurry vision and sometimes weakness in the face if affects the cranial nerves. Here, I just show a few other examples of how ADEM can look like.

[00:08:01] There's always... There's a sense of pattern recognition, but a lot of times they can look different, even between cases that we call ADEM. This first example showing a bit more kind of fluffy, less well-defined borders, a bit more symmetry in the right and left halves of the brain. Here the borders are a bit more distinct, and the lesions appear smaller but still are a good larger size, a centimeter or 2 or greater.

[00:08:28] These first two show white matter involvement, but it can go in the deeper gray matter parts of the brain, as depicted here. And in the cases where the inflammation may have proceeded very rapidly or aggressively, the tissues can be very significantly injured, and bleeding can result in the most affected areas. In the cases that there's some maybe diagnostic uncertainty, children and adults have gotten biopsies of the brain to see what's going on, on a microscopic level.

[00:09:02] And here, the... I'm trying to use my cursor. The areas that I'm showing you are veins, and the purple dots are all these immune cells that are congregating around the veins, that really shouldn't be there. And in the cases where there's too many of them and they're calling all their friends to come in and they're secreting a lot of chemicals that can lead to injury, we have demyelination, which is what's shown here.

[00:09:29] The blue is the myelin. That's usually around the white matter in the brain. And here are areas where that myelin is obliterated, essentially. So, a lot of things have come from how we've defined ADEM in the sense from the International Pediatric MS Study Group that proposed these criteria in 2013. That this is a first-time event. A previously healthy child most of the time. Multiple symptoms that we can see based on our exam and through imaging. Encephalopathy or that kind of change in awareness and behaviors that's not explained by some sort of ongoing illness.

[00:10:11] The MRI has to be abnormal by definition, and it shows that pattern, some of those examples that I alluded to. And a real major key in saying that this is ADEM and not something else is that the child should, by and large, get better after this event and that they don't have any further relapses or new episodes of inflammation 3 months after this initial presentation. As we've understood these conditions better, we've refined the way we've been able to test for a specific disease or specific ideology to ADEM.

[00:10:48] The main important one, which I think you'll hear from other talks throughout this symposium, is anti-MOG related syndrome. Aquaporin-4 is another type of antibody that the body can make that can affect parts of the brain that overlap with ADEM, but generally it does not have that encephalopathy or that acute change in mental status. Because infection is something that we would treat differently and would not want to miss, a lot of the initial laboratory testing is to make sure that this is not an infection, in which the immune system is activated, but helping the person by trying to fight off the infection.

[00:11:26] We have to use... We often use antibiotics and antimicrobials simultaneously as we're treating for ADEM if we're not sure at that beginning stage. Spinal fluid will show elevated white blood cells in the majority of cases, and elevated protein, which usually indicates that there's some sort of injury in the integrity of the blood-brain barrier and the proteins in the central nervous system.

[00:11:53] These are some other things that we might look at to look at alternative diagnoses, such as multiple sclerosis, in which we may see oligoclonal bands. And there may be types of stroke or other mass lesions where we may get increased pressure, that overlap with ADEM. If a child is very sleepy or unresponsive, we may do a brain wave test of... to look for seizures or to document abnormal functioning of the brain.

[00:12:28] And, again, in the very beginning stages, we really want to make sure we're treating the right thing by ruling out the things that can look like ADEM. Like many of the other conditions that have been presented through the symposium, we use the same types of first-line treatments. IV steroids because it's easily accessible and it's really quick to start it, and those are general kind of just dampening signals to immune system that we want to settle the inflammation and try to stop the swelling.

[00:13:02] We often will start thinking about other second-line or therapies after IV steroids, such as plasma exchange that tries to filter the blood of any antibodies and inflammatory signals in the blood. Or give antibodies to help the own body stop making maybe disease-causing antibodies, or flush out the system of disease-causing antibodies. In many cases of ADEM, if a child does better, we still want to not necessarily take the steroids off cold turkey, but send them home with an oral taper that may last anywhere from a month to a month and a half, usually. Again, most people do well, but they may spend a few weeks in the hospital and get rehabilitation, either in the hospital setting or outpatient.

[00:13:51] About a quarter of them will require ICU level care, and this usually relates to breathing difficulties, really depressed level of awareness, where we're worried about if they can protect their airway, if they have seizures. And it's really important to support someone because inflammation can be treated with our regimens, but we want to make sure that they don't suffer any sort of kind of complications of being so critically ill and not being able to be able to think clearly.

[00:14:25] And then, as we... As a child is able to become more alert and aware, we hope that therapists, such as physical, occupational, and speech therapists, can help with encouraging their recovery. So, for the prognosis, over time we've learned about how to recognize this condition, starting treatments early. It's very rare for a child or a young adult to die from ADEM, thankfully, and many of them make a pretty big recovery within the first month after diagnosis.

[00:14:54] I know many people will get an MRI of the brain 3 to 4 months after just to see sort of what the fallout of that was, and in many cases, those lesions may get significantly better or almost nearly resolved. As we look... Take a deeper dive in sort of how mood, thinking, development of a child is affected, it seems like there may be more lasting symptoms in fatigue, headaches, learning difficulties, may be kind of a sequela of ADEM.

[00:15:27] And in up to a third of cases, we do see recurrence, and because now we understand more about MOG-related syndromes, we know that that is often the underlying cause for that. So, yeah, the distinction of 'is this a one-time episode where it kind of behaves like we would expect ADEM, that a child gets better, never has another attack,' versus something where there are more episodes, either episodes that fit criteria for ADEM or episodes that may just affect the optic nerve or just the spinal cord.

[00:16:01] You can get one past in terms of having one more ADEM episode, but if you have another attack after that and if you have attacks that don't meet criteria for ADEM, we typically try to call it something else, whether that's multiple sclerosis, NMO, or some other demyelinating disorder that we're still not sure of. And then, yeah, MOGAD has been probably the most revolutionary thing in the last few years in terms of kind of pillaring our understanding of ADEM.

[00:16:33] We can test for this in the blood, and it's a pretty good test that there's not false positive or false negatives. And that does help us in many ways in counseling a family, because we can see this antibody being quite high in the beginning, but over time it usually goes down. And in cases where it completely disappears, we can usually tell those families and children that it's unlikely they would have a relapse.

[00:16:59] But this doesn't take away from a really important part of our job here, which is to support the normal typical development by locating any sort of long-term deficits in thinking or mood or behavior, and then providing accommodations to the family and schools so we can optimize that person's outcome. The same way if you have a problem with movement of your arms and legs and you would need physical therapy, a big part of ADEM is offering cognitive and behavioral therapies to support typical development of thinking and mood regulation.

[00:17:40] So, we definitely partner up with our psychiatrists and our neuropsychologists and psychologists for that. Monitoring for relapses, and in cases where it is deemed to be something that could be relapsing, providing therapies to decrease the risk of ADEM occurring again or some other demyelinating syndrome is important. So, hopefully, that'll give us some time. Let me stop sharing, so I can see if any questions have filtered in.

[00:18:07] **Krissy Dilger:** Thanks so much, Dr. Wang. Yes, we did get one question regarding MOG positive ADEM. "Are there any trends that might help predict whether a child will be monophasic or not?"

[00:18:23] **Dr. Cynthia Wang**: Yeah, that's a really great question. There's been a lot of articles that have started to address that question, and it seems that how quickly and how dramatically that MOG antibody titer, and somebody listed titer there, decreases within the first couple of years seems to be really important. We typically see most kids decrease that number after, the colon is, kind of suggest how high it is in the blood. So, it's not surprising in the case of this other... this family member, that it starts really high and then over a year or two, it goes down.

[00:19:07] It's still not consistent how long we should check this. I usually check every 6 months for probably the first couple of years just to see what the trajectory of that titer decrease is. If it goes to zero, I think that seems to suggest that the immune system has learned its lesson, it's not making these antibodies, and it's unlikely that child would have another attack. But in rare cases, it can go to zero and a person can have an attack. There's cases where somebody has a titer that's persistent, but maybe low, and never has attack, even after 10 to 20 years. So, I think the jury is a bit still out, but I generally can provide some reassurance if that antibody goes down quickly and if it disappears.

[00:19:58] **Krissy Dilger:** Great. Thank you. Oh, so this person is... Their child, it seems, has loss of vision. So, is that... What is that in correlation to ADEM? Is there anything you can provide context on with that or if that's common or any kind of treatment?

[00:20:24] **Dr. Cynthia Wang**: Yeah. Let's see. Yeah. It's often quite striking how severe the vision loss with MOG and MOGAD can be. A lot of times it can decrease quite quickly, where a child may not be able even to see motion or even see light. Typically, if we get steroids and we do things like plasma exchange, we can reverse that, but it's not uncommon still to have some problems with visual acuity. This person is mentioning 20/20 is normal vision.

[00:20:59] So, it seems like their daughter is struggling with having difficulty with distinguishing visual acuity. Yeah. I would say that can be the case if it's quite severe and if there's some delayed treatment. At our center, if somebody is not able to see motion or light, we really start the thought process for plasma exchange soon, and it seems that that overall might lead to better outcomes.

[00:21:31] Yeah, I would say the first probably 3 to 6 months is when we see that vision come back, and then we're kind of left with, I think, what the fallout with the tissue injury is. So, luckily with MOG, it doesn't seem

like the visual impairments are as significant as NMO-related Aquaporin-4. But yeah, it can certainly be quite limiting, so we want to work with the families and the school to make sure we're providing children ways of being able to see things in bigger text or listen to things to help relieve some of those potential deficits.

[00:22:15] **Krissy Dilger:** Okay. Thank you.

[00:22:16] **Dr. Cynthia Wang**: Yeah.

[00:22:17] **Krissy Dilger:** Oh, sorry. There was anything else you wanted to add or?

[00:22:20] **Dr. Cynthia Wang**: No. Yeah. Yeah, and it's hard to say. I think... Yeah. Sometimes how we tailor our thoughts about do we put somebody on immunosuppression is also how bad an initial attack is. If you had bilateral... both of your eyes were severely affected, sometimes that will lead us to counsel families different on, 'do we put somebody on a medicine to try to prevent another attack?' Because it would be quite devastating if you had physical impairments or significant visual impairments after a first or second attack.

[00:22:58] And then it looks like there's a question about a foundation to disperse. Well, I think just being part of this symposium, what the Siegel Rare Neuroimmune Association is doing is really helpful. Certainly, we hope that these symposiums engage not just patients and families, but providers. And that you can tell them, for somebody who may not know about these conditions, you provide the website to the SRNA, and they can be kind of a proponent of your child and family by looking into these conditions.

[00:23:35] And if they feel like this is too subspecialized for them, there's a list of providers, I think, that you have available. So, you can have consultations with people like me, who see more of this. Yeah, and I think the way families can help is just, yeah, to share information about these conditions. And it seems like we're building that network with all these conferences and podcasts and other types of educational media. Yeah, I think COVID has thrown a wrench in some of more of our engaging in-person events, but hopefully this at least is widening our reach. So, people who have an Internet connection and they can look at this material, kind of now don't have an excuse not to learn a little bit more and try to understand it better.

[00:24:29] **Krissy Dilger:** Great. We did get a question about treatments and their effectiveness depending on the timing. So, can you kind of just go over the importance of how quickly or how important it is to receive acute treatments quickly after? Does it make a big impact? What's the time frame that you can actually administer these treatments after the inflammatory event?

[00:24:57] **Dr. Cynthia Wang**: Yeah. I think, hopefully, most of the time ADEM looks so concerning and it progresses to a point where families get worried because their child is not behaving appropriately. That pretty quickly we're able to get imaging that confirms the diagnosis. So, ideally, we would see IV steroids get started within a day or two with children presenting to an ER and getting that imaging. The center's practice in terms of things like plasma exchange and IVIG is more variable, partly related to just equipment and personnel.

[00:25:37] We're a big center that we like to do PLEX if we know that there's significant impairment in things like walking or there's significant vision impairment. So, I think we tend to just have a kind of lower threshold to start those treatments. But yeah, usually ADEM, except for those very severe cases, can respond very well to steroids alone. So, sometimes I'm actually having to dial back some of our trainees, that we don't need to go to PLEX right away. We can take a few days, see how the 5 days of steroids go. So, in case of things like MOG, yeah, the steroids seem to be really sufficient in many cases in reversing a lot of the deficits.

[00:26:22] **Krissy Dilger:** Okay. Thank you. We got a question about vaccines and, "Is there any evidence or research going into possibly the correlation between vaccination and an ADEM attack?" I'm just curious to hear your thoughts.

[00:26:38] **Dr. Cynthia Wang**: Yeah. ADEM, I think was initially called postinfectious or postimmunization, postvaccinal encephalomyelitis. But that's probably decreased a lot with improvement in how we make vaccines. They used to make vaccines, like the rabies vaccines, there would actually be neural tissue in the vaccines. So, you can imagine if you inject somebody with brain tissue, that could probably be triggering to the immune system to make a response to what's in it, and that's not the case anymore.

[00:27:15] But yeah, I think there is less known, if like... If your immune system is primed to sort of overreact because of genetics, could an infection trigger that? Yes. We... Could a vaccine trigger it? Perhaps, but I don't want to make that assumption that just because you got it, that was what caused. Things that trigger the immune system maybe lead to ADEM, but from all the data we've had from other diseases, like measles, from this year of looking at COVID, there's a dozen or more reports of COVID-associated ADEM.

[00:27:55] I think I've only seen one in which there was a temporal association with the vaccine, and you have to imagine, a lot more people have gotten the vaccine this year than have contracted the illness. So, yeah, it's not impossible, but I think it's a numbers game. So, that's when... When I counsel my families of patients who've had this, I almost unanimously say, "Get vaccinated," because you would not want to get the infection and that would be a much stronger stimulus to the immune system.

[00:28:26] **Krissy Dilger:** Okay. Thank you. I think we're just about at the end of our time. But I really... We really appreciate you joining us and volunteering your time and expertise on this topic. And hopefully next year we'll be in person, but just so happy to be able to at least put on this event and be able to bring in people from all over the world.

[00:28:47] **Dr. Cynthia Wang**: Yeah. Thank you so much for the invitation. Yeah. And then, feel free to reach out to me if any questions come in. I'm always happy to come back and talk and do podcasts and so forth. But yeah. Take care, everybody. Enjoy the rest of the symposium.