APERTURE

What Have We Learned About ADEM?

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

[00:00:00] **Roberta Pesce:** Welcome back, everyone, for our next talk. I am joined by Dr. Cynthia Wang, Assistant Professor at the University of Texas Southwestern and 2016 SRNA James T. Lubin Fellow. And she is here to give us a little update on the APERTURE study on ADEM. Hi, Dr. Wang! Welcome. Over to you.

[00:00:27] **Dr. Cynthia Wang:** Okay. Thank you very much, Roberta, for the introduction, and thank you to the Siegel Rare Neuroimmune Disorders Association for inviting me. It's always a pleasure to talk to your audience, so yeah, we'll dive in about APERTURE, which is a study I've been doing to look at some characteristics of ADEM. And I will say, yeah, I was the very lucky recipient of a James T. Lubin award that helped me really gain this training and understanding of neuroimmunology and ADEM, and as many things are in this field, the therapies aren't FDA-approved. So, it will be done off-label.

[00:01:07] I'll just go through a quick introduction. And I apologize, I haven't been able to tune into the symposium as much. I've been in the hospital on service and it's interesting because these rare conditions I've actually seen at least two patients with one of the conditions that the SRNA serves, so I think rare is really a relative term. But yeah.

[00:01:28] I'm not sure if other people have talked but I'll try to give a quick introduction of ADEM, so everybody is on the same page before we go into some of the research. So ADEM stands for acute disseminated encephalomyelitis. And those words, if we break them down don't seem quite as scary; sudden, widespread inflammation of the brain and sometimes the spinal cord. This myelin injury or myelin swelling within the nervous system can lead to abnormal functioning of the brain and the spinal cord.

[00:01:57] The $1 million question for all these conditions is why does it happen to certain people and not to others, and we think it's probably a combination of somebody who's genetically vulnerable and something in the environment that triggers an immune process that is dysfunctional and abnormal. So perhaps there are some infections that resemble proteins in our body, and then our immune system gets confused and starts attacking parts of our body. That's the general understanding and when it is ADEM, and the brain is the target of a lot of that attack you can get any of these symptoms that I have listed.

[00:02:36] In terms of who gets ADEM, I'm a pediatric neurologist, and this is primarily a pediatric disease. It affects boys and girls about equally, maybe a little bit more commonly in males. Usually that early school age, grade-school age is the key demographic, a few cases per million children a year and it seems to strike more in times of the year where we're indoors and we're spreading germs. So, the clinical presentation just really depends on where in the nervous system the inflammation occurs, if we ask questions about you know, were there anything preceding these neurological symptoms.

[00:03:18] Sometimes we find out that the child had an illness and pretty insignificant respiratory or a viral illness in the weeks before, and then as they developed the neurological symptoms, sometimes we'll see fever, headache, nausea, generally not feeling well. And then depending on the extent and the location of the inflammation, we can see signs of irritability, sleepiness, weakness or numbness, bowel or bladder dysfunction or vision loss and eye pain.

[00:03:51] The acute treatments are similar for the other conditions that have been discussed not really backed by you know, the gold standard type of clinical trial data but a lot of smart predecessors have used these types of treatments and seem to be helpful for this condition including high dose IV steroids, plasma exchange and IVIG. And typically, a child will go home on a steroid, oral steroid that gradually ramps down over several weeks. So, the typical hospital course is a couple weeks, and some individuals can be sick enough that they need to be in the ICU for help with breathing or support for stopping seizures.

[00:04:34] Sometimes there's really significant brain swelling that requires very close monitoring and neurological exams. Once we start the medical therapies, we also want to think about starting the physical, the occupational, and speech therapy because part of this is also to try to regain those skills that may have been lost with the inflammatory attack. Prognosis is generally thought to be quite good for ADEM that children with this condition improve within a few weeks and that is shown and demonstrated by subsequent MRIs which those abnormal areas of inflammation and lesions can be completely gone, but I think if we take a more detailed look, there are probably more persistent cognitive and mood symptoms that can be only noticed after a child has gone back to school, or had increasing demands of normal life placed on them.

[00:05:37] We're still looking at if children who've had ADEM have normal rates of growth of the white and grey matter in the brain. Up to a third of the time after initial ADEM, there still can be a recurring attack, either of ADEM or some other demyelinating syndrome, so that was something I certainly was very interested in, and while overall people who get this condition do well, up to 3 percent may die so I think it is still nothing to be light or flippant about.

[00:06:09] So a couple years ago at the 2019 RNDS I kind of presented these were some of the thoughts or some of the just impressions of ADEM that was already kind of being toppled. And I think in the years since then we've also found out a lot more about different subtypes of ADEM but just to kind of challenge these beliefs, ADEM just the one-time event or one-time inflammatory episode. It doesn't relapse. ADEM is a benign illness. People do well, they go back to doing what they were doing.

[00:06:44] And then that like the other conditions we study we categorize it as a demyelinating, or primarily a white matter disease. The result is this pesky part of the ADEM classification which you can get ADEM twice and we still call it ADEM or multiphasic ADEM. But generally, if there are more attacks or there's another type of attack that's not ADEM, we call it something else, but I think this gets to the fact that you know maybe there are different types of conditions that we lump into one group that we are in the past do not know what they were composed of. So, I think that was always an area of quite a lot of interest.

[00:07:29] And now we know about MOGAD, so MOG, or myelin oligodendrocyte glycoprotein antibody disease, it's frequently present in children and young adults who have acquired demyelinating syndromes. We know that it's not the same disease process as multiple sclerosis or neuromyelitis optica-related to aquaporin-4 antibodies. And that you can get these spectrums of symptoms, ADEM being one of the most common ones specially seen in younger children.

[00:07:56] You can have optic neuritis that is recurrent or bilateral; you can get inflammation of the spinal cord, that overlaps with other conditions but may have distinct features which I'll discuss. And that yeah in this syndrome we can follow this antibody out and for people who have persistent MOG antibodies, they are at risk of relapse. So just a little bit about what MOG is. It's a protein on the outer surface of myelin. It's made by the myelin-producing cells called oligodendrocytes.

[00:08:29] Later in the life cycle than most other proteins, so there's some speculation, is this something the immune system isn't really used to because it develops later, it's been known as early as the mid-80s. But really, it's in the last 5 to 10 years that we've been able to test for it reliably and accurately, so really has driven this field forward. And then with this really valuable biomarker, for MOG, this antibody test in blood, we've been able to increase sort of our understanding of the whole spectrum of conditions that MOG antibody disease can lead to, including encephalitis, where it looks more like seizures, behavioral changes, a meningitis-like picture.

[00:09:22] It can be really big lesions that in a pediatric neurology world we think of genetic and metabolic conditions. It can disproportionately affect gray matter in some cases. And it can lead to you know, very significant acute changes such as increased pressure in the brain at the onset of the condition.

[00:09:47] I guess this gets to the idea that ADEM is a benign condition, and we know that this isn't true because there were other subtypes or conditions that were sort of lumped into ADEM that can lead to tissue injury, tissue death and hemorrhage, and some of these, we've found that genetic predisposition with different mutations can make this more likely in certain people when they have a viral infection.

[00:10:18] So here are a few images of the patient that I took care of a few years ago, and you can tell from how much the extent of the kind of the brightness in this brain. This is all swelling, and this was a 5-year-old boy. He had the symptoms that we usually see at the initial onset of ADEM, he had quite a significant decline where he was not responsive and required intubation in order to protect his breathing, and then this was a very striking MRI that showed diffuse edema or swelling of the brain.

[00:10:58] So I think this is one of the things that, which keeps me up at night with some of these ADEM patients is that we have a lot of medicines that can stop the inflammation and help that go in the right direction to recover function but there are some things that we can't alter, which is the space inside the skull. So, during that acute period where there's a lot of myelin edema and swelling, we can see in cases such as that child where there's only so much space, if brain increases in size and other things get pushed out, such as blood or spinal fluid, or parts of the brain itself if there's too much pressure.

[00:11:39] And I think a lot of the real big complications that come from a child who has ADEM is that swelling, if that's not adequately managed while we're waiting for steroids and plasma exchange to take effect then there can be some irreversible injury. And those are definitely the saddest cases that I've seen and then also as pressure goes up your heart is pumping blood. You're pumping almost uphill if the pressure in the brain is very high. So, it's almost a double whammy of badness when this happens. Okay.

[00:12:14] And then ADEM is a white matter disease. We know that with conditions like MOGAD, parts of the brain such as the deep gray matter can be affected and then parts of the spinal cord where we expect more of the gray matter can be affected. So, here's a child we saw that had this very striking MRI in the spine. Limited primarily to the gray matter and this reminds us, of other conditions such as acute flaccid myelitis, I think this is really important because children who present like this may be misdiagnosed as acute flaccid myelitis, but they have MOGAD, and they can really benefit from things like IV steroids and plasma exchange and IVIG.

[00:12:58] So being able to start to tease apart these conditions at the onset before we get that confirmatory MOG is really important. So, most of the time even if a child looks like acute flaccid myelitis I still try to treat pretty aggressively because this is still an alternative diagnosis. So, this boy had difficulty walking, urinary retention, things that were a little atypical for AFM is that he did have intact reflexes and he had that sensory level. And yeah, lesions in parts of the brain that we did, typically don't see AFM affect.

[00:13:34] Alright, so with that I think because these are rare conditions, I learn a lot from the individual cases, but really, we want data to drive decision making and how we structure research and treatments, and management of people who are coming in with this illness, so I hypothesize what we call ADEM is composed of different disorders. We wanted to evaluate how a patient's initial features can impact the long-term outcomes and then use neuropsychological testing to discover maybe the more subtle cognitive deficits related to ADEM.

[00:14:15] So during the years, I think about three years we were recruiting, we had 37 children that initially met criteria or were diagnosed as ADEM. With an average age of 5 1/2 years. This was disproportionately male in this cohort and then I'm in Dallas, Texas so actually looking this up this is pretty similar to the composition of our population here, with the exception of lower percentage of Hispanic, and I think that's because a lot of the neuropsychological tools are only standardized in English, so families had parents that were primarily Spanish-speaking, they did not qualify for this trial. But I think the rest of this data is pretty in line with what we know from the prior literature.

[00:15:09] So with the initial presentation of ADEM, it was much more common to have a simultaneous spinal cord involvement than optic nerve involvement. MOG positivity was about half of these patients. Half we tested, we kind of take all comers who are tested, but some of these people were seen, hospitalized before we had the good MOG test, so if I just limit it to the people who are tested at the very earliest presentation of ADEM it does go up a little bit. So that is a really considerable population of ADEM. The relapse rate in this cohort was about 24 percent and we followed children on average about five to six years.

[00:15:50] Looking closely into who initially had the ADEM criteria and who really met criteria, I found a few that seemed to have better alternative explanations, acute flaccid myelitis being one, cerebellitis, where there was inflammation just in only one part, not that widespread multifocal inflammation and then another child went on to be diagnosed with multiple sclerosis. And I'll say that nearly three quarters of these patients were treated here at UT Southwestern, and that probably has a lot to do with the types of therapy that were given. We are a big plasma exchange center, so almost a third of the patients got both IV steroids and PLEX. Other cases they just got steroids alone. IVIG was used with steroids about 20, 19 percent of the time, and then some children went on to get all three.

[00:16:42] So and then in terms of children that had relapses or were placed on immunosuppressive therapies, that was about a quarter and here are a few of the medications I found that were used. These add up to more than nine because some people had to go from one to the next and do a few more in order to control their disease. This is the tragic part about ADEM, that some people really do poorly in the acute period and they suffer really significant brain injury, so one of the patients in this cohort died related to complications of ADEM,

unfortunately, and then there's more that I need to comb through in terms of the neuropsychological testing and the patient-reported outcomes but generally, in the patients that did go on to have neuropsychological testing, 90% of them seemed to on average have normal full scale IQ.

[00:17:40] So in summary, ADEM, we currently define it by clinical features, imaging features, but really, we're moving toward a molecular, more specific diagnosis, and MOG being one of the most common specific diagnoses of ADEM. The outcomes are generally favorable but then cases can be life-threatening, lead to long-term disability or be associated with relapses, and then I think really understanding there are 50% of what makes up ADEM will help us develop more effective and targeted treatments for these conditions. So with that I'd like to thank the SRNA for inviting me. I'd like to thank some of the wonderful people I get to work with on a daily basis and thank you for your attention.

[00:18:24] **Roberta Pesce:** Thank you so much, Dr. Wang for this wonderful talk. We've got some questions from our community. So, the first one is, what's considered persistently positive when it comes to MOG?

[00:18:36] **Dr. Cynthia Wang:** Yeah, I guess persistently may be thought of like how high it stays or how long it stays. What I generally do is like MOG every six to 12 months. And it's been, I think this is a changing topic in the field but generally, the first year to two years that antibody level will drop and then at some point it may just stay at a low level, or it may fluctuate but in a number of kids maybe as much as 50 percent it goes away within the first two years. And that's usually a good sign that they may only have a one-time attack of demyelinating, of demyelinating symptoms.

[00:19:23] **Roberta Pesce:** Okay and the other question that we received is, is the onset attack typically more severe than a relapse?

[00:19:30] **Dr. Cynthia Wang:** No that's a really great question. I think a few things are in our favor when it's a relapse because we already know that a child is at risk. Hopefully a doctor has counseled the family, these are the other potential symptoms you can see with a relapse. We have plugged in with the clinic and with a physician who hopefully would be starting things like steroids and other interventions faster. So, I think the disability from relapses is generally lower because we don't have to go through the process of knowing what we're treating.

[00:20:02] **Roberta Pesce:** Yep. And another one just came in. Does IVIG affect MOG test results?

[00:20:08] **Dr. Cynthia Wang:** Yeah, no, that's a really great question. And that MOG titer that level of MOG in the blood is often something that now that we're sending it so much sometimes, I see a MOG titer, and I don't know if it explains the child's illness. So, it kind of depends on how high it is. If it's a kid coming in with ADEM that number is really high. It's something like one to 10,000 or one to a thousand.

[00:20:31] Sometimes I get results like one to 20 or one to 40 and if it doesn't really otherwise make sense with ADEM or MOGAD, with MOGAD, then sometimes I'm inclined to not take that at face value so hopefully in the general population there's not that many people with MOGAD. That's where IVIG comes from blood donors, so I think if it's significantly high, maybe over 1 to 100, then I think you can trust that result is the child's own body producing the MOG.

[00:21:02] **Roberta Pesce:** Okay. Okay. Well, thank you so much for taking the time and being here with us today. We really appreciate it. It was great. Yeah. Great talk.

[00:21:13] **Dr. Cynthia Wang:** My pleasure!

[00:21:14] **Roberta Pesce:** Thank you so much.

[00:21:15] **Dr. Cynthia Wang:** Take care, everyone. Take care.

[00:21:16] **Roberta Pesce:** Thank you.