APERTURE:
New Insights on ADEM

You can view this presentation at: youtu.be/bAT5q36kM9s

[00:00:01] **Dr. Carlos A. Pardo:** We are ready for our last lecture. After that we are going to have a period of question and answer so be prepared with your questions because that is the last opportunity, we will have for exchanging information about many of the concerns that you may have. Again, it's a great pleasure to introduce now, Dr. Cynthia Wang, who is another of the next generation of neurologists who is going to be working in the next several decades on myelitis, myelopathy, and immunology. Dr. Wang also was a former SRNA fellow. Again, SRNA helps us to train neurologists in the area of neuroimmunology, rare neuroimmunological disorders, myelitis, and myelopathy. When you are donating to SRNA that money is going to be supporting many of these young doctors who are going to be the future of neurology. Dr. Wang is a neurologist who trained at UT Southwestern with Dr. Ben Greenberg and obviously she has the energy of Dr. Greenberg as well. She's going to talk about new insights on acute disseminated encephalomyelitis. Cynthia, thank you for being with us.

[00:01:38] **Dr. Cynthia Wang:** Well, thank you everybody who is still here. I am very impressed with your grit and tenacity in staying this long. It's been a wonderful conference I can't thank the SRNA enough for putting it on inviting me. I feel humbled to be in the midst of such greatness. I will talk about findings from a study of ADEM that I did starting in my fellowship and have continued, and a lot of this data is pretty new, so you're getting hot off the press updates. First, we haven't talked about ADEM too much I think it's been mentioned in the context of other conditions like MOGAD but just so that everybody's on the same page this stands for acute disseminated encephalomyelitis. If you break down that very long name, it means basically sudden and widespread inflammation of the brain and the spinal cord. As you might imagine this may lead to a lot of different neurological symptoms that may cause different types of lesions in the spinal cord and the brain. A key defining feature of this is something called encephalopathy and that's a fancy word for saying that someone's not acting like themselves, they may be tired or confused or irritable. But it can progress quickly to other things like lethargy and coma. As a pediatric neurologist, I appreciate this condition since it does affect children far more than adults. There usually is some sort of triggering event typically infection.

[00:03:12] The management of ADEM parallels a lot of the acute treatments we have for the other rare neuroimmune conditions, so high dose IV steroids, plasma exchange, IVIG. Oftentimes if patients doing well, they still go home with a tapering dose of oral steroids I think something that's very important to know about ADEM is that these children or young adults can look very sick in their beginning stages in their presentation.

About a quarter of them need ICU level care because they may be too obtunded that we're not sure that they will be able to breathe on their own or they may have refractory seizures that are quite scary. Thankfully most people who have this condition make a significant improvement within a few weeks. Some may go on to require inpatient or acute rehabilitation, others can do okay with outpatient rehab, but therapies are really important to regaining function. What's lesser known about long term impact of these conditions but has been alluded to in smaller studies is that there are lasting mood, cognitive, motor sensory deficits and if we really look, we find evidence of that. I think there were a few tenants or concepts that I learned about ADEM when I was in training that it should be a one-time illness, monophasic illness that doesn't relapse.

[00:04:44] I was also told that it's relatively benign, it doesn't cause much injury, people do find that you wouldn't even know that somebody had ADEM. Then like other demyelinating conditions we think of it mostly as a white matter disorder. But I think we've known in recent years that that's not true MOG antibody disease has clearly proven that it can relapse. I've seen personally unfortunate cases where there were very life-threatening complications of ADEM and in the literature there are reports of those as well, very aggressive fulminant subtypes of ADEM. In the studies I've done with patients, there's often even more disproportionate gray matter involvement in certain parts of the nervous system such as the spinal cord, but it certainly can affect both white matter, the cables, the wiring, as well as the gray matter more the cell bodies and the command stations of those neurons. I think a big change and shift in this understanding came from our increasing understanding of MOG antibody disease, myelin oligodendrocyte glycoprotein. The unique features of this protein are that it's expressed on the outermost surface of myelin. It is also produced relatively late in the development of myelin. I think for these two reasons it might lead the immune system to get bogged down by it because it has access to this protein and then it may not recognize it as self because it doesn't get exposed to it earlier on. Then testing from MOG antibodies has been really increasingly available and reliable in the past five years, so I think that's really helped characterize this population.

[00:06:33] I'll shift gears and talk about APERTURE which stands for assessment of pediatric and adult encephalomyelitis related outcomes, understand, reveal, educate. It was a play from CAPTURE, the TM study. My hypotheses included that ADEM, like the work that Dr. Pardo has done with TM, like we've known for other diseases, that it's probably composed of separate conditions and the more we take a deeper dive into ADEM we'll be able to find out what those are. Then I wanted to see if there were early features of a person's presentation, their laboratory testing, imaging, or other factors that can help us understand what the long-term outcome for the recovery of this condition might look like. We took pretty much all comers under the age of 65. I had to have availability to review the records because some of these surveys and neuropsychological tests are only validated in English, we're limited to speakers of English or proficient in English and excluded only people who during their first attack of their illness the diagnosis may have changed to something else that had to be ADEM.

[00:07:53] We recruited from the summer of 2017 to the end of 2020 and I'm so grateful for all the people who trusted us to review their records and put in time for some of the surveys in these studies like Dr. Blackburn alluded to it was often if you weren't seen at our center to get records. I think for the sake of cohesiveness of this dataset I'm presenting just the children who were seen at Children's Health in Dallas, and we were able to also test MOG antibodies for. This represents the entire cohort, it's a group of 37 children, you'll see that about half of them were MOG positive and half were MOG negative. The caveat of this data is that some of them were only tested later on because prior to 2017 we didn't have that technology. I think important and relevant in the MOG negative group because perhaps those people were originally MOG positive and then later when we could test them converted to MOG negative.

[00:09:03] The average age I think is similar to what's been described in past reports about 5.5 years, give or take three years. There was a slight male predominance in this entire cohort and the racial distribution was

pretty similar to what I think has been reported in what we see in our clinic with the exception that there's probably some Hispanic individuals that we cannot enroll in this study. Looking more specifically at the MOG positive cohort, you'll see this very little skewed towards slightly older population. I think it was interesting to me, this seemed to be a more even split between male and female sex, the race ethnicity was pretty similar to the entire group. Then for the MOG negative group they were slightly younger, I think it's interesting. I think most of the MOG literature does suggest it's pretty evenly split male and female, so you have to wonder this historical description affecting more males and ADEM if it comes from maybe this this MOG negative cohort and the race ethnicity was pretty much the same as the whole group. The MOG test is great. I think we've put a lot of value in it. Unfortunately, it takes 2-3 weeks to come back, so I chose to look at some of the other studies that clinicians may have at our disposal earlier on to make decisions about care and that includes things like spinal fluid testing.

[00:10:44] One thing that we look at is something called number of nucleated cells. It gives you a sense of how many white blood cells or immune cells are in that spinal fluid space where they really shouldn't be. Under five is considered normal and defining high range is 5-50 and very high is greater than 50. For the MOG positive cohort, you'll see the majority, or the greatest proportion of those people were in that 5-50 cells per cubic millimeter range. In the MOG negative group, I think the point that stands out to me most is that there were some patients that didn't seem to have a very inflammatory looking CSF. Again, I think that indicates that a subset of that population might have a condition that doesn't quite behave the same way we think of ADEM as fulminant inflammatory condition. Then we definitely make the diagnosis of ADEM it's assisted by neuro imaging. So, a few ways I wanted to break down how we view this is to look at where lesions are predominantly or exclusively in white matter, gray matter, or a mixture of both. Here you see two examples of the white matter that's bright in this image being affected.

[00:12:07] Here are two other images where these deep brain structures the thalami had involvement and then this is a mixed pattern where you both have deep gray structures as well as some white matter involvement. I put them side by side because in the first column these are all MOG negative patients, and the second column is MOG positive. Even though I think there's a lot of differences in MRI, I would think it would be hard based on just looking at the pictures for one clinician to differentiate the two. I thought that was an interesting thing that I noticed. Looking at specifically whether MOG positive, the composition of this distribution, the vast majority of children with MOG antibody disease had a mixed picture, so both gray matter involvement and white matter involvement. In the MOG negative group, it was also quite mixed pattern, but it seemed like there was a subset that had more exclusively white matter involvement. Another way to break down how and where this disease occurs is to look at the structures. I broke this down into brain only, brain and optic nerve, and brain and spinal cord. None of the individuals had all three parts of those structures affected.

[00:13:31] In the full group about half of those people had brain involvement only. I would say probably the key difference and again, I haven't run the statistics on this to know if the statistical significance, it seemed the MOG negative groups skew toward more simultaneous brain and spinal cord involvement in the beginning. I alluded to how sick these kids can get, and I think this is really important because a lot of the morbidity can happen during the early stages of the acute attacks, so I wanted to see what percentage of that group needed ICU level care. Then another way to look at how sick these kids are is how much of the swelling and the inflammation led to increased intracranial pressures. Sometimes if these get too high then people can have life threatening consequences. You can imagine if you sprained your knee, it's okay, your tissue is pliable, things can expand but your brain is encased in a pretty rigid box, so any additional brain swelling can lead to serious consequences. In the full group, about 40 percent needed ICU level care at our institution. In terms of neurosurgical or medical intervention for increased ICP that's about 14 percent. Then I also wanted to see after the acute treatments, the steroids, plex, IVIG, how many people might need further acute rehabilitation and that was about 22 percent.

[00:15:08] I'll show you when we look at the MOG positive group. In the MOG negative groups, ICU stays percentages were similar. Interestingly and I think this does reflect my own personal experience, the MOG positive kids they really struggle with increased intracranial pressures. We sometimes get an indication while we're doing the lumbar puncture that they have something called an increased opening pressure. But I think a fairly sizable subset of these patients really needed some acute interventions to bring that pressure down. Then the rates of rehab immediately after the ADEM was pretty similar between those two groups. Treatment, I'll put out here. I think it's very institution dependent and I think ours is one that does plasma exchange a lot more than many other pediatric hospitals. But you'll see that in all three groups it seems like steroids and plasma exchange was the most common regimen that they received. I think this is really important, once your child has been diagnosed with MOG, what are the chances they may have another attack? Because I was taught that it shouldn't come back. In the group as a whole, there was about a 24 percent of a relapse within the average of 6.6 years of follow up. That was higher in the MOG positive group, about a third and lower in the MOG negative group.

[00:16:37] I'm hopeful that other groups will contribute and replicate this data and I think it does parallel with what has already been known. Then I've listed some of the immuno-therapies, some patients had to try more than one, but this just gives you a global idea. At our institution which medicines we use; I think starting out we did a lot of rituximab it slowly shifted more towards IVIG for MOGAD. Then interestingly a few of our MOG negative patients had a phenotype that was very similar to MOGAD. They had maybe ADEM and then later had optic myelitis or transverse myelitis. These were cases that were really surprising to me that they were MOG negative. I wonder if there's a different myelin antigen that they might have a response to. Then some keen people who know MS drugs might see that there's an MS drug. This was a child that I think eventually had the phenotype more of multiple sclerosis but started as ADEM. Then I think the saddest part of my job about this seeing these kids is that sometimes their acute disease is so terrible, and they have such a protracted hospitalization that they do succumb to their illness.

[00:18:00] I won't go over this too much because I think Dr. Harter had mentioned a lot of these things but the majority of the subjects who did undergo comprehensive neuropsychological testing scored in the average range that's about 90 percent. Of the ones that I did see that had lower scores that was composed of one MOG positive patient and two MOG negative patients. I put the ages because I think that is important, that's something that's been reported on. Some groups have found that the earlier when you have ADEM maybe you might have more long-term cognitive consequences and that makes sense intuitively. If you've never learned the language your mind is still forming and then you have this event at a critical age that that might affect cognition and emotional regulation more. I think this leaves me with the question, what is MOG negative ADEM? I think for the time being we'll probably refer to it as idiopathic, meaning that we don't know the underlying cause but still suspect that an infection triggered some sort of immune reaction that was overexuberant.

[00:19:11] In terms of thinking about alternative diagnoses, I'll give you a few examples of imaging from people in this group. This was interesting. When I was looking at neurosurgical interventions, this child ended up getting something called a Chiari decompression. You can see from the line actually I have a pointer here. Usually, the part of your cerebellum which is this structure, shouldn't go below the line that I've drawn here and his did dip quite a bit. He was diagnosed with a Chiari one malformation and then this was also significant enough to cause something kind of a cyst to form in this spinal cord called the C ring. I have suspicions that hearing from other people in the TM community that have also picked up on this association, that there may be something to Chiari's, some predilection to developing these conditions. Usually, we do MRIs about 3-4 months after ADEM just to see have the lesions resolved and gotten better.

[00:20:20] This was a child that really their lesions didn't get much better and I think it makes me think if he could have an alternate diagnosis such as some sort of white matter disorder. Then this one shows the child during ADEM, but you can tell that maybe if you've seen enough of these MRIs like I have that these ventricles the fluid structures of the brain are too large. He I think already had an existing genetic diagnosis, so it makes me wonder whether some genetic conditions give you, like Dr. Jafarpour talked about, maybe confer some increased risk of neuroinflammatory disorder. These people weren't part of the APERTURE cohort, but I just wanted to put this as an example. This is a young lady who had nausea, vomiting, imbalance, and was initially called ADEM. She ended up having a condition called lymphomatoid granulomatosis. This is a rare Epstein-Barr virus triggered lymphoproliferative disorder which is a type of cancer. Here's another patient who also was initially called ADEM. This was a three-year-old girl that became very sleepy was hard to arouse. We treated her as if she were ADEM, didn't get any better and she ultimately was diagnosed with melioidosis, I practiced this. I just don't know how to say it. It's a bacterial infection caused by Burkholderia pseudomallei, I actually find that easier to say than the other name.

[00:22:05] Then this is a patient I followed closely. He was very puzzling to me because he had COVID and then he had ADEM and he responded to the medicines, but he was very recalcitrant to treatment, every time steroids came off things got worse again. Eventually I had him on IVIG and rituximab and that seemed to hold down his symptoms. Then his younger brother had a similar presentation, and we did genetic testing at that point, and he did have a condition called CNS familial HLH, that you just heard about. His mutation was different than the ones presented but it was a mutation, and something called perforin that has to do with our breaks or checkpoints of immune activation. Getting back to the theme of APERTURE, I think this was my view of ADEM before this project and before my training and I'm hoping that as we learn more about these conditions, it can grow to a bigger view. We might recognize a significant subset of ADEM to be MOG antibody disease, some other auto-antibody diseases that maybe are currently unidentified, a subset of this is probably infections that we never were able to test or track them down, perhaps some genetic brain disorders, different types of rare cancer disorders, and then hopefully a smaller subset of this will be considered idiopathic or we don't know why it happened.

[00:23:29] So, in summary MOGAD antibody disease seems to make up a significant portion of kids that we diagnosed with ADEM. Generally, they have good outcomes but there is certainly a possibility of life-threatening complications due to the degree of brain swelling and acute stages of the disease, and relapses can occur. Then in ADEM without MOG antibodies, I suspect that this is made up of a heterogeneous group of many conditions that requires further study and characterization. I think the more we dive deeper into what we call ADEM we'll be able to find more targeted, effective strategies, better ways of surveillance of these conditions, and also long-term strategies if necessary. With that I'd like to thank that SRNA again. I have some of my colleagues here, Tricia Plum was our research nurse, and she's been so helpful with this project, but I'd like to thank all of you also for your attention.