Clinical Analysis of Children Presenting with ADEM with or without MOG-IgG

You can view this presentation at: youtu.be/O4i_x1s4o88

[00:00:04] **Dr. Linda Nguyen:** Thank you for inviting me to give a presentation on my work on children with ADEM, with or without the MOG antibody. The room already is fully aware, ADEM stands for acute disseminated encephalomyelitis, which means a rapid onset and widespread inflammation of the brain and spinal cord.

[00:00:30] And so, ADEM can occur across the lifespan, affect really anyone, but it predominantly affects children. It typically presents as a monophasic attack or one-time attack, and it's associated with multifocal neurological symptoms, including vision loss, numbness, weakness, gait changes, and bowel-bladder dysfunction. A key feature of ADEM is encephalopathy, which is a clouding of consciousness.

[00:00:58] In kids, this can present with behavioral changes like irritability, fuzziness, somnolence. They can also have confusion and seizures. There's no blood-based biomarker for ADEM exactly, but we know that a subgroup of patients has the MOG antibody. And so, the study aim was to characterize, in children presenting with ADEM: 1. The clinical and paraclinical features, that is the imaging and laboratory data. 2. The outcomes that may be associated with the MOG antibody or without the MOG antibody.

[00:01:34] And so, in trying to determine the differences, at least at presentation, this can potentially help clinicians when a patient come in with ADEM, whether they're likely to be MOG-positive or not before the test comes back. Because the test can take two to three weeks before it returns, and so, knowing it earlier on may change potentially the way we manage patients in the acute setting. In addition, depending on what the differences are, it can point to us a unique pathophysiology that maybe we have not realized yet. And in the second part, looking at the outcomes in the long-term follow-up, this can help us better manage patients and guide families through the recovery process.

[00:02:23] I included patients seen in the demyelinating disease clinic at Children's Health in Dallas. I included patients that were seen between 2017 and 2024. 2017 is when the MOG antibody first became initially, commercially available for testing in the United States. They had to have a diagnosis of ADEM, and they had to have testing for the MOG antibody at disease onset. This is because, if you have MOGAD or MOG antibody disease, this is the optimal time for testing the antibody.

[00:02:58] I was able to identify 38 children that met these criteria, and the majority of them or 71% of them had the MOG antibody, and 29% was MOG negative. And so, looking at these two groups, what I found is the MOG-positive group typically presented at an earlier age of onset, a median of five years compared to eight years of age. And then, I've put stars next to several data points on the talk that may be notable or had significance on statistical analysis, just to bring your attention to it a little more.

[00:03:37] In terms of the sex breakdown, there wasn't a difference between the two groups. Something notable was that, typically, we think of the MOGAD as a disease that didn't have any gender predominance, but at least in our small group here in the ADEM cohort, there may be a male predominance. In terms of the race or ethnic backgrounds, there wasn't a significant difference, perhaps a little more percentage of patients with MOG-negative ADEM being of Black or African American race.

[00:04:14] Now, I'm looking into the acute phase, looking at the clinical and paraclinical features between the two groups. So, looking at the presenting symptoms -- really the clinical symptoms they came in with -- typically, ADEM or commonly ADEM can be referred to as a post-infectious encephalitis, meaning there was a preceding viral infection or infectious trigger in a lot of the patients. You can see here in both cohorts, the majority of them had some preceding infectious symptoms, maybe a slightly more in the MOG-positive group than the MOG-negative. In terms of whether they had seizures or not, pretty similar, maybe a little more in the MOG-negative group.

[00:04:57] And then, in terms of vision changes, it's really only the MOG-positive group that reported any vision changes, about 20% reported changes, where 0% in the MOG-negative group. And in line with this report of vision changes, when you look at their MRI, there's optic nerve involvement really in the MOG-positive group only, seen in 36% of the patients compared to 0% in the MOG-negative.

[00:05:24] The MOG-positive group also seemed to have more spinal cord involvement. Then, we looked at all types of MRI features, but one thing we were really interested in is a finding called posterior globe indentation. So, what is that? If you look on this image here of the MRI of the brain of one of the patients we had. So, you see the eyeball, and behind the eyeball or the globe, there's the optic nerve coming back on the backside and connecting to the brain. The arrow is pointing to the area of indentation or flattening of that globe. Usually, it should be a curve or rounded.

[00:06:08] And so, what this is just above is, there's increased pressure behind the eye, building up and pressing on the back of the eye. So, there's increased pressure in the brain. We are able to see this on MRI really only in the MOG-positive cohort. We worked closely with a pediatric neuroradiologist, and we asked him to try to score the lesion burden on the MRIs for these kids. And so, he gives a score for each area of signal abnormality, and also, depending on the region and how much involved it is, the higher score. And so, the left side shows the different scoring for different areas. And then, the right side really just gives you the cumulative score in terms of lesion burden level: low, medium, high, or very high.

[00:07:04] And so, when we look at the MOG-positive cohort, looking at the level of high and very high lesion burden, this made up of little more over 50% of the patients, whereas it was only about a third of the patients with MOG-negative. So maybe, this suggests that there is a greater lesion burden in the MOG-positive cohort. MRI is essential for the diagnosis of ADEM, but we also looked at cerebral spinal fluid analysis because this can help support the diagnosis and also rule out other causes. And so, in the spinal fluid, you can look at the total nucleated cells, which are just essentially the white cells or the immune cells that may be active and causing inflammation.

[00:07:49] You can see, if it's abnormal, it's greater than five for this study. So, the MOG-positive group, the overwhelming majority of them, 96%, had elevated white count or total nucleated cells. Again, the majority of patients of MOG-negative patients did too, but less so. And then, we looked at also the protein count, but there wasn't a difference between the two groups. One of the things that you can do or measure when you obtain a lumbar puncture is, measure the opening pressure. So, in pediatric patients, if you have an opening pressure greater than 28, that's considered high. And what this means, it's a marker for increased intracranial pressure.

[00:08:37] So, if you recall, I said, with that posterior globe indentation on MRI, it was only found in the MOG-positive cohort. It seems also, in terms of opening pressure being high, that was also only found in the MOG-positive cohort. So, two markers suggesting of increased intracranial pressure only in the MOG-positive cohort.

[00:09:00] We also look at just their overall course, how they did in the hospital. It seems like they stayed in the hospital for a similar duration of 13 days. In terms of needing ICU care for whatever reason, it's pretty similar, maybe a little higher in the MOG-negative group. In terms of functional impairment, looking at the inability to walk without assistance, it's pretty similar, maybe a little higher in the MOG-negative group.

[00:09:25] And finally, in the last column, again, going back to the idea of the increased intracranial pressure, in terms of requiring some management for it, whether that be medical or surgical interventions, the MOG-positive group seem to have a little higher percentage of that.

[00:09:43] And in the hospital setting, they receive acute treatments in form of different immunotherapies. We brought that up a little bit in terms of what the standard of care is for ADEM. And so, that can involve steroids or steroids in a combination with IVIG or plasma exchange. And in this data point, it looks like in the MOG-positive group, they're more likely to receive plasma exchange or PLEX.

[00:10:10] So, really, the steroid and PLEX group was 30%. All three is 22%. So, if you total it together, it's about more than 50%, whereas in the MOG-negative group, only about a third or a fourth of them receive plasma exchange. So, what does that mean? Usually, we resort to plasma exchange when they may have a more significant functional impairment. So, in a way, it's a marker of disease severity.

[00:10:42] And then, that's in the hospitalization period, but what happens afterwards when they follow us in clinic? Is there a difference between the outcomes in these kids with the MOG antibody or not? And so, in terms of outcomes, it looks like the MOG-positive patients tend to follow with us for a longer period of time -- 23 months instead of 12 months.

[00:11:02] And then, in the literature, it seems to suggest that if you have a MOG antibody and present with ADEM, you're more likely to relapse; but in our cohort -- at least our small cohort -- there wasn't a difference in relapse rate. And in terms of looking at ongoing symptoms affecting function, a pretty similar rate, maybe a little more in the MOG-negative group.

[00:11:27] We also took a look at their MRI in the recovery phase. We had the MRI in the acute phase. Llooking at the recovery, because we often obtain the MRI three to four months after the attack, just so we can get a new baseline. We anticipate a significant resolution of those signal abnormalities, or T2 lesions, as they're called.

[00:11:50] And so, interestingly, we found that the MOG-negative group, a 100% of them, had complete recovery or resolution of their MRI findings, whereas only 43% of the MOG-positive group did.

[00:12:08] And then, in addition to obtaining an MRI of the brain at least once in the follow-up period, we like to obtain an OCT, or Optical Coherence Tomography. So, this is a really useful test because it's quick and non-invasive. A kid just has to stand in front of this machine here, stare into the lens, and look at a light. Then, we're able to take a picture of the optic nerve, as shown here on the right.

[00:12:36] And really, we can get to the almost the individual cell-width level, the micron level. This shows the different layers of the retinal layers that the OCT can capture. And really, we're focusing on the nerve fiber layer, which, in optic neuritis or inflammation of the optic nerve, you can get thinning of this layer over time. And so, the OCT gives a report, and this is an example of the report.

[00:13:02] So, it gives a quantitative value of the retinal nerve fiber thickness. And so, in our kids that had OCT and had completed the test, we can find that, really, it's only the MOG-positive patients -- 50% of them -- had some abnormal thinning of that retinal nerve fiber layer compared to the MOG-negative group. And so, this is just a little more than we would expect, just based on symptom report of vision changes and MRI findings of optic nerve involvement.

[00:13:37] So, this suggests that the OCT is a more sensitive test for picking up prior optic nerve injury. And so, in summary, just to wrap this up and give our impression is: at presentation, it's important to note that in a MOG-positive cohort, they were more likely to have increased intracranial pressure, they're more likely to have optic nerve involvement, and they're more likely to have elevated total nucleated cells.

[00:14:06] So, maybe, they have a more inflammatory disease process than the MOG-negative cohort, perhaps. And follow-up for whatever reason, I'm not sure why yet, but the MOG-negative group seemed to have more complete recovery on their MRI than the MOG-positive group.

[00:14:24] In terms of ongoing symptoms affecting function, the MOG-negative group slightly had higher rate of that. Relapse rates were similar. And, importantly, the OCT was only able to detect abnormal thinning in the MOG-positive group.

[00:14:41] So, what this means is: if a clinician is suspecting a patient is presenting with ADEM and it's MOG-positive because they have optic nerve involvement and elevated white count in their spinal fluid analysis, then they should be cognizant that they're at risk for increased intracranial pressure, because the management of that may be different than just giving them immunotherapy. And in the follow-up period, it would be useful to get an OCT, if able, because that can pick up on prior nerve injury more than just based on clinical symptoms or prior MRIs.

[00:15:23] And so, thank you for your attention, and I'd like to thank these people: Dr. Greenberg and Dr. Cynthia Wang for being my mentors during my fellowship, and, really, the patients who were seeing them while I was tagging along. And Dr. Singh, who's the pediatric neuroradiologist that looked at all the MRIs, and Darrel for the OCT. All right. With that, I'll take any questions from the audience.

[00:15:59] **Audience Member 1:** Thank you so much. You mentioned in your MOG-positive population that there was a very high percentage of patients with preceding infections. Do you have any clue what type of infections were those? Are those upper respiratory infections, viral diseases, diarrhea, enterovirus? That's question Number one.

[00:16:20] Question Number two: Do you show an MRI which there is this sign of optic protruding, but you mentioned that your interpretation is increasing intracranial pressure. Can be the other alternative explanation is papillitis in MOG?

[00:16:45] **Dr. Linda Nguyen:** Great question. So, in the first one, I didn't exactly look at the type of symptoms they were presenting with in terms of the infectious symptoms -- whether that localized more to the respiratory symptoms or GI symptoms -- but, in practice, I think it's more respiratory symptoms. I've seen no specific infection or virus, but it seems to be more the respiratory in the ADEM cohort.

[00:17:12] And then, in terms of the globe indentation: the question of papillitis, we tried to look at that. I wouldn't imagine, if it was that, to also have involvement of the optic nerve in terms of signal changes, and we're able to see that even despite no optic nerve involvement. So, I think, in correlation with -- or at least in line with -- the opening pressure measurements, it may be more suggestive of just increased intracranial pressure than the involvement of the optic nerve.

[00:18:02] **Audience Member 2:** Hi, how are you? I actually have a question. You mentioned that you really didn't look at symptoms, but maybe you have an opinion just on your observations. Were there particular symptoms that were different between the MOGAD-positive or the MOG antibody disease patients who had ADEM and those who were MOG-negative when they were experiencing a relapse.

[00:18:28] In other words, some parents that we talked to at the MOG project, they talk about behavioral issues being one of the first signs of relapse. I wondered if there was any difference in what patients and parents experienced when a child was entering into a relapse?

[00:18:50] **Dr. Linda Nguyen:** Yeah. That's a great question. To try to see if there's a difference in presentation after the initial attack. I didn't specifically look into that. In our cohort, there was a very small percentage of patients that even had relapses, for really just 20%. So, I'm not sure. I can take a look at those patients to see, but it's very small numbers to make any guess into the pattern.

[00:19:21] **Audience Member 3:** Okay. Hey. Sorry. I'm going to try to make this make sense. Okay. So, you mentioned the PLEX, and steroids, and IVIG, and stuff. Have you all seen anything that shows that if you do PLEX first, like steroids or whatever, would it possibly keep some of the deficits down and maybe prevent further disease activity? Maybe, if that's the way I mean to say it.

[00:19:56] He never had PLEX, but I feel like he should have. He went on to have a VP shunt and all kinds of other stuff. He's had a lot of cognitive delays, and I'm wondering if maybe, if we had done that, it would have changed any of these outcomes.

[00:20:13] **Dr. Linda Nguyen:** Yeah. It's hard. Well, I can say that there's no study that proves plasma exchange is going to improve outcomes in terms of rigorous designs, but it seems like, not necessarily in the ADEM cohort, but at least I know in the optic neuritis cohort, if you give plasma exchange earlier on, usually within a week, and improve visual outcomes.

[00:20:38] So, if we try to connect it to ADEM, perhaps the earlier initiation can improve outcomes. On an individual level, it's hard to say, but we like to give plasma exchange because we do think it improves outcomes.