Increased Intracranial Pressure in Pediatric MOG Antibody Disease

[00:00:02] Krissy Dilger: Hello and welcome to the SRNA "Ask the Expert" podcast series, "Research Edition." This podcast is titled "Increased Intracranial Pressure in Pediatric MOG Antibody Disease." My name is Krissy Dilger, and I moderated this podcast. SRNA is a nonprofit focused on support, education, and research of rare neuroimmune disorders. You can learn more about us on our website at wearesrna.org. Our "Ask the Expert" podcast series is sponsored in part by Amgen, Alexion, AstraZeneca Rare Disease, and UCB.

[00:00:42] For this podcast, we are pleased to be joined by Dr. Cynthia Wang and Dr. Linda Nguyen. Dr. Wang is a neurologist at the University of Texas Southwestern Medical Center and a former James T. Lubin Fellow. Dr. Nguyen is a neuroimmunology fellow at the University of Texas Southwestern. You can view their full bios in the podcast description. Welcome and thank you both for joining me today. To start us off, Dr. Wang, can you provide a brief explanation of what MOG antibody disease is?

[00:01:17] Dr. Cynthia Wang: Sure. Yeah. So, MOG antibody disease, or MOG antibody-associated disease, MOGAD we've termed just for speediness. It's a primarily—think we mostly know this as central nervous system acute demyelinating syndrome, though sometimes peripheral nervous system involvement has been noted. We know that it's distinct from multiple sclerosis and Neuromyelitis Optica associated with aquaporin-4 antibodies, though it can present similarly with symptoms of vision loss or weakness. The diagnosis hinges on detecting MOG antibodies, primarily in the blood.

[00:01:55] And MOG is a protein on myelin and myelin-producing cells. And there are certain clinical syndromes that we associate with it. Classically, it's been acute disseminated encephalomyelitis, particularly in younger children. Kind of across the board, children, and adults, we see optic neuritis, myelitis, or spinal cord inflammation, is another manifestation. And as we've had these tests that have allowed us to do more investigation in other syndromes, we've found that brain inflammation, including in just the cortex where seizures may be the primary manifestation or parts of the brain such as the cerebellum, the brain stem, or isolated parts of the brain where you don't get the encephalopathy or the kind of the change in mental status we see with ADEM, is also possible.

[00:02:46] One of the things I like to tell families is, you know, it's one of the demos that I like giving because it doesn't often pretend necessarily a chronic or relapsing condition like multiple sclerosis and NMO. There're different data sets, but probably a third to half the time, if we follow these patients long enough, we'll see a relapse. But typically, if recognized quickly and treated quickly, the likelihood of disability is low. And I would say, yeah, the research has really accelerated in the last five years with the commercial availability of the testing. And just earlier this year, International Consensus Group came up with the first proposed criteria for MOG antibody associated disease. So, yeah, I think it's an exciting time to be in this field and looking at MOG.
Krissy Dilger: Awesome. Thank you for that overview. And, yeah, I agree it sounds like an exciting place to be for the future. Dr. Nguyen, how did you become interested in researching MOG antibody disease?

Dr. Linda Nguyen: As Dr. Wang was alluding to, it's distinct from multiple sclerosis and NMOSD associated with aquaporin-4 antibody. And it's most recently described as the CNS demyelinating disorder. So, while there's increasing knowledge on its various clinical presentations, it remains a disease that there's a lot left to be studied, including what factors at onset may be associated with long-term outcomes, especially if you have a monophasic disease course or a relapsing disease course.

And then I think another feature I was particularly interested in is because, different from MS and NMO, which predominantly affects adults, MOGAD can affect children in up to 50% of the reported cases. And then so while it's a rare disease overall, it makes up a substantial portion of the patients we see in our pediatric neuroimmunology clinic.

Krissy Dilger: Got it. Thank you. And we're happy that you are interested in researching this disorder because it is rare and newer, as we mentioned before, and it's important that we learn more when we can. So, can you talk about the background of this study? What led to the development of this particular research study?

Dr. Linda Nguyen: Yeah, so, there's a few small case reports or case series mentioning increased intracranial pressure in patients with MOGAD. And by "increased intracranial pressure," I'm saying there is increased pressure inside the skull around the brain. And because this is a closed system that comprises a fixed brain tissue, blood, and spinal fluid volume—if there's increased pressure in this compartment—this can lead to brain damage or spinal cord damage because there's pressure on the important structures. And so, this can add to the injury that's already being caused by the inflammation from the underlying disease process.

And so, we were noticing that a good number of our patients had increased intracranial pressure. And there were questions arising on how do we, like, manage these patients. And so, we carried out this particular research study to, one, determine the frequency of increased intracranial pressure in pediatric patients with MOGAD, and then, two, to evaluate the association with increased—or of increased—intracranial pressure with long-term outcomes.

Dr. Cynthia Wang: Yeah, and I think it's—just to echo off what Dr. Nguyen said, I think intuitively, it would always be, like, these young patients that were very obtunded, meaning that they weren't responding, they often need to go to the ICU for management of breathing because their mental status was so depressed. And yeah, I think that there was this sense that if it's a young person with very acute onset of very widespread inflammation that they tend to do poorly. And when we didn't have some sort of objective measure to go on, in terms of knowing what was happening in the brain, whether we did neuroimaging or we had some other measure to measure increased intracranial pressure. It just seemed like we would be flying without a compass or any navigational tools, I guess. It can sometimes feel like, it's like we have this precarious plane that we need to land and then, if you don't have any of those tools, then it becomes really hard to know what you need to do to get somebody through that. So, I think it's just amazing the work she did to put some objective numbers and see what our institution's experience has been. So, yeah, great work.

Krissy Dilger: Awesome. And so, what would you say is the broad research question this study was attempting to answer, Dr. Nguyen?
[00:08:07] **Dr. Linda Nguyen:** Yeah, we were just really trying to figure out if there was a difference in outcomes between patients that had elevated opening pressure, which is indicative of increased intracranial pressure. And by “opening pressure,” I was referring to increased opening pressure on lumbar puncture. And then compared to patients that had normal opening pressure and seeing if there was a difference in outcomes there. And then directly asking if, for the patients that required management of increased intracranial pressure, how was their outcome on an individual basis?

[00:08:49] **Krissy Dilger:** Got it. Thank you. So, how was the study set up? Was it retrospective, number of patients, that kind of thing?

[00:08:59] **Dr. Linda Nguyen:** Yeah, so this is our own institution’s experience, and this study was done retrospectively. We included about 86 pediatric patients that met the diagnostic criteria for MOGAD as recently proposed by the International Consensus criteria. And then we reviewed their clinical data from the first attack and then their long-term outcomes at last follow-up. The MOGAD patients that were included specifically were those that had increased intracranial pressure based on opening pressure measurements and/or those that required any intervention to help offset or decrease that intracranial pressure at their first event.

[00:09:53] And then, as I mentioned, we define “increased intracranial pressure” for the group analyses based on the lumbar puncture results. When you do that procedure, you can have opening pressure obtained, and that can help serve as a proxy of what the pressure is in the central nervous system. And we define “elevated opening pressure” as greater than 28 centimeters of water.

[00:10:26] **Krissy Dilger:** Got it. And so, Dr. Nguyen, what were the findings from the study?

[00:10:34] **Dr. Linda Nguyen:** Yeah, so, in our cohort of 86 patients—and we found that, of all those that had lumbar punctures done, about only 50% of them had opening pressure obtained. And so, we’re working with a smaller cohort here. And then of these 50% of patients, 21% had elevated opening pressure. So, that made up about nine patients total. And so, of the nine, seven had ADEM or acute disseminated encephalomyelitis. One had optic neuritis, and then one had another phenotype that wasn’t ADEM or optic neuritis.

[00:11:22] And so what we found in our group data was that in those with elevated opening pressure greater than 28 centimeters of water, these patients were more likely to require an ICU stay, required medical or surgical interventions to help reduce intracranial pressure. They had longer hospitalizations, longer outpatient follow-up duration. And importantly, we found that they were the higher proportion with increased disability, long-term.

[00:12:07] And then we also noted, you know, because MOGAD can present with many different presentations, of the nine that had elevated opening pressure, the majority of them were of the ADEM phenotype. And then, so that’s in the group analysis. So, in the individual like case-by-case analysis, looking at patients who actually received any medical or surgical interventions (“medical” meaning, like, they had to undergo some hypertonic saline boluses to control their sodium level or be suppressed with phenobarbital or required surgical, neurosurgical, procedures), we found that six of them had ADEM and one of them had a presentation called cortical or cerebral cortical encephalitis.

[00:13:08] And so, I mean, overall, in these patients, these seven patients that require all these medical or surgical procedures, you know, they had all various outcomes, and their clinical course in the hospital was all very different. But what was noticeable is that, on long-term outcome, all of them had neuropsych data available, and all of them had at least some deficit identified. So, what this all means overall, what we found
was, overall, 21% of patients with MOGAD, especially those with ADEM, had increased intracranial pressure. And then, this was associated with a greater utilization of healthcare resources and worse long-term outcomes.

[00:14:02] **Krissy Dilger:** Got it. That’s very interesting and something that is good to know, and I’m sure will have implications moving forward. So, which leads me to my next question. What do these findings mean from pediatric MOGAD patients and how they may be treated upon onset of their disorder or in the disease course? Dr. Wang?

[00:14:30] **Dr. Cynthia Wang:** Yeah, I think the results are all, you know, I think, very hopeful to know where we need to go next. When I have conversations with families, I’m typically pretty optimistic, but I think this—especially the kind of—the data is like, generally people do well after ADEM, and they make a recovery. But then it’s always like, what happens to that 10 or 20% that don’t do well? And I think we now have more definite characteristics of what those patients might look like in terms of their demographic features, in terms of this ADEM phenotype and what they might look, you know, in the initial few days of being in the hospital, needing to be in the ICU and maybe needing other supportive services.

[00:15:08] So, yeah, I think it really helps piece together what are the factors for long-term disability in MOG. For many of these conditions, we often wonder about, like, accrual of disability with relapse. But I think if you don’t help mitigate potential disability at the very onset, then that becomes a moot question. So, yeah, I think—so these situations also kind of have some interplay with how we maybe decide and decide on the order or the sequencing of acute therapies.

[00:15:44] I think one thing that comes to mind is that we always want to do the most aggressive thing. We give the IV steroids, we want to start plasmapheresis, and just throw the kitchen sink at patients. What Dr. Nguyen is mentioning is that we need to maybe sometimes put on other hats in terms of not just being the neuroimmunologist and reaching toward our immuno-therapies, but thinking about other things that are very important to the physiology of patients such as getting proper oxygen and blood flow in the brain and intracranial pressure, I think, plays a big role in knowing how to make those decisions.

[00:16:22] So, I think early consideration and awareness of what medical and surgical interventions may be needed is really helpful, and any tools that we can develop to provide some sort of practiced guideline so that we are more consistent about getting opening pressure, or we know early to involve the neurointensivist or the neurosurgeons. So, yeah, I think all those things are really critical, and it’s definitely a jumping-off point for further studies.

[00:16:56] **Krissy Dilger:** Awesome. And so, kind of like you said, for further studies, this question is for both of you, do you anticipate future iterations of this study will develop? Dr. Wang, do you want to start us off?

[00:17:16] **Dr. Cynthia Wang:** Yeah, I think whenever we talk about retrospective data, it’s going to be automatic to say, “Let’s do a prospective data,” so we can be a little bit less biased about the sampling and things like that. So, I hope this could be something not only our institution, but other institutions, start to look at. And again, I think if we do find that some of the tools, whether it’s doing the opening pressure, looking at invasive and non-invasive ways of measuring ICP such as with ICP monitors, our center uses other tools such as pupillometry.

[00:17:54] So, I think finding what are good ways to assess this and follow those changes over time are really important. And yeah, I hope it just sheds light that this is more of a team effort—that it’s not just consulting with the neuroimmunologist, but also knowing different aspects of how the patient is doing. You know,
we—sometimes we don’t think about vital signs and like chemo dynamics as much as other groups do, and I think that becomes really important in this situation.

[00:18:27] Yeah, I think those are definitely some of the things. And yeah, you know, the brain is an enclosed box. So, there's only so much we can do if the swelling is outpacing our ability to treat it. But if we can draw that process or spread that inflammation to absorb potential damage in different ways, I think that can be helpful to outcomes.

[00:18:53] **Krissy Dilger:** Definitely. Dr. Nguyen, do you have anything to add?

[00:18:56] **Dr. Linda Nguyen:** Yeah, those are really good points. I think we, based on our experience, have noticed the increase intracranial pressure, we’ve noticed that more in MOGAD patients, but it's not exactly clear if this increase intracranial pressure is unique to MOGAD or other CNS demyelinating disorders like multiple sclerosis or aquaporin-4 NMOSD. And so, I think next, at least what we've been trying to do is, to explore this further, is implement routine measuring of opening pressure for all patients presenting with sinus demyelinating disorder.

[00:19:38] So, that as I was mentioning, only 50% of our patients had opening pressure measured. And so, trying to make it more standardized can maybe increase that percentage and allow us better to study, increasing intracranial pressure overall. And I think this, along with the clinical exam, the neuroimaging, can allow us for early stratification of risks for patients requiring either ICU care or, and/or neurosurgical consultations much earlier in their disease or their presentation. And hopefully, earlier awareness can improve outcomes.

[00:20:30] **Krissy Dilger:** Well, great. Thank you so much, both of you, for taking the time today to answer my questions and hopefully help our community learn about this research that's going on because I think it's really important, and it's great to have this access to this information for people who are affected by these disorders. So, thank you again for joining me, and hopefully we can continue the conversation.

[00:20:57] **Dr. Cynthia Wang:** Thank you, Krissy. Always appreciate the invitation and, yeah, being able to share the things that we're working on.

[00:21:07] **Krissy Dilger:** Thank you to our “Ask the Expert” podcast sponsors Amgen, Alexion, AstraZeneca Rare Disease, and UCB. Amgen is focused on the discovery, development, and commercialization of medicines that address critical needs for people impacted by rare autoimmune and severe inflammatory diseases. They apply scientific expertise and courage to bring clinically meaningful therapies to patients. Amgen believes science and compassion must work together to transform lives.

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