Research Updates

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[00:00:00] **Dr. Grace Gombolay:** We're gonna talk about some of the research that we are doing here at Emory and Children's Healthcare Atlanta. And first I'm hoping that Dr. Kannan can come up and talk about some of the work that we're doing in children.

[00:00:16] **Dr. Varun Kannan:** As we all know, rare disease research is hard because these diseases are rare. We just need numbers and patients to get confident data and that's really hard, especially in kids. So, networks that connect different centers are really important because that's how we pool all of our data and patient information together and learn about these diseases together.

[00:00:40] So I wanna briefly talk about one of these patient networks which is the National Network of Pediatric MS centers. So initially designed for research in multiple sclerosis, but they've actually expanded to include a lot of the disorders we talked about today. So ADEM, MOGAD, NMOSD, transverse myelitis, and optic neuritis and kids all falls within the purview of this network.

[00:01:01] Grace and I both trained did residency and fellowship at places that were part of this network. Initially started with six centers but has now expanded to 12, I believe. And we are very excited to be part of that network now officially as of last year. So, a couple of different goals of this network.

[00:01:17] One of them is basically a registry. So, we collect patient information about the diagnosis, how the presentation happened, how the diagnosis was made, what treatments we tried, and then which ones worked. So, we've been treating kids with these rare disorders for a long time, several years, even though we don't have FDA improvement, FDA-approved treatments because we pulled some data together and found out things like in pediatric N-M-O-S-D, we know that rituximab actually is safe and effective.

[00:01:46] Similar with MOGAD, we know that IVIG is safe and effective. So even though we don't have trial data yet, we have very confident data that says these are treatments that we should be using in kids, even though it's off label, which makes the insurance battle challenging, but we've gotten better at navigating that as well.

[00:02:03] And then a couple of areas looking to the future. For example, there's a question right now. Like I said earlier today in kids MOGAD is usually monophasic, which is a one-time attack that may not ever relapse

again, but some kids relapse. So, one of the questions that's being asked right now nationally is what if we did a short-term treatment with IVIG for let's say six months?

[00:02:25] Does that prevent the chance of a subsequent relapse happening? That's a really important, interesting question. So, the network is trying to answer that right now. A couple of areas looking far in the future. So, one we touched on this as well, is how does that gut brain immune access that I mentioned play a role in these disorders?

[00:02:42] Are there specific diets that can offer benefits versus harms? If you're living with these disorders. And then the farthest in the future. And probably the most important question is we call remyelination. So, we have a lot of really cool drugs, including the ones that these panelists before us talked about.

[00:02:59] What these drugs do is control relapses and we're getting better at controlling relapses. What none of these drugs do is heal neurological damage. That has already happened and as of right now, we don't have any approved technologies or treatments that do that. We need to look into that because that is an important thing.

[00:03:16] If you're living with this it's great to control relapses, but we all want to see healing improved. So that is a kind of far distant but very important area of research that the network is looking at.

[00:03:30] **Dr. Grace Gombolay:** Great. Thank you very much Dr. Kannan. And I know you have to leave but thank you very much for being part of today.

[00:03:35] **Dr. Varun Kannan:** Happy to be here.

[00:03:37] **Dr. Grace Gombolay:** Next. I'm hoping Dr. Hutto, can you talk about some of the work that you've been doing on the Emory side?

[00:03:42] **Dr. Spencer Hutto:** Yeah, sure. So, yeah, I'm on the adult side and we have a few projects I think that overlap with some of the disorders that we've talked about in this room. So, the first thing that, we look at on the hospital side of things, because I'm very interested in diagnosis and how do we treat relapses when patients come in and how do we improve their chances of getting back to the way that they were before the attack occurred.

[00:04:06] because that's very relevant to working in the hospital setting. And so, we discussed earlier how plasmapheresis has really been a great treatment for patients who have NMO in terms of the acute relapses and applying plasmapheresis sooner tends to have a bigger effect. And so, one of the questions we've had for MOG since that is also a disorder associated with an antibody that would be susceptible to the effects of plasmapheresis is would that also be useful in patients who have NMO?

[00:04:32] There's been several studies that have shown that it's very helpful or sorry, in, in MOG, but there have been several studies that NMO that has shown that it's been effective. Yeah. Could we do the same thing in MOGAD? And in the recent timeframe, there has been a study published from multiple centers that show that that patients get better when they use.

[00:04:52] Plasmapheresis if they have MOGAD in addition to steroids. That was a study that was conducted across several dis, several different sites in the United States and also, I think some, places abroad. It didn't have a comparator arm though to see how patients who received just steroids alone versus those who got steroids and plasmapheresis did.

[00:05:10] And so that's one of the questions that we're looking at in association with some colleagues who are at the University of Pennsylvania. And so hopefully we'll have that data fully ready to be submitted maybe by the end of the month, and we can get some better information about is this treatment worthwhile beyond just really the effects of steroids.

[00:05:26] And so that's interesting for the MOGAD group in the room, I primarily see patients who have neurosarcoidosis in clinic. And one of the questions that I always have is how do I differentiate that from some of the other disorders that present similarly? And so those things include multiple sclerosis, MOGAD, and NMO and, sometimes being able to identify what you're up against early can mean that you can institute treatment faster.

[00:05:51] And we just spoke about how plasmapheresis sometimes can have a bigger effect can have if it is applied sooner. But if it's the first attack that you've had and you've come into the hospital you can send antibodies and sometimes those things will take anywhere from four to seven days to come back.

[00:06:07] Obviously as a clinician in the hospital, we don't wanna sit on our hands for four to seven days to make a decision about treatment that could really affect how somebody does over time. And so, one of the things that, that we're interested in is figuring out if there is some specific signature on MRI that could be used to differentiate perhaps earlier.

[00:06:28] Which disorder a patient is, more likely to have, because plasmapheresis, like we said is really likely to help NMO or preliminary data for MOGAD suggest that it's at least helpful for the optic neuritis form of, MOGAD. That is probably not gonna have much effect at all actually in patients who have neurosarcoidosis is the sense that I have.

[00:06:47] And so how do we use our resources appropriately and early? There are other treatments for patients who have neurosarcoidosis that perhaps we could use, earlier. And so, what we are trying to do for optic neuritis is determine if there's a certain way that it appears on MRI that we could use to differentiate sarcoid versus.

[00:07:04] Multiple sclerosis versus NMO versus MOGAD. And so that's a shared overlap space. We are also doing a lot of work in neurosarcoidosis, and most patients will sometimes have optic neuritis, and they can have transverse myelitis. And so, it can have manifestations that are similar to a lot of the disorders that we've talked about today.

[00:07:21] We're doing some work to figure out what may give us some ability to predict how patients do when they have transverse myelitis related to sarcoidosis. Because some patients have a mild attack and some patients have very severe debilitating attacks. And so, we're doing a deep dive in terms of what was it about their presentation, what sort of symptoms they had, how long it took them to present or to obtain a diagnosis.

[00:07:51] What did their blood work show their spinal fluid testing results? What did their MRIs look like? When were they treated? How long did it take to get treated? And are any of those variables predictive in terms of how a patient does over time? And so, we're looking into that and, who knows, maybe that sort of information can be applied to some of the other disorders that we've talked about today in terms of how do you model prognosis?

[00:08:11] Because one of probably the most challenging question that I get actually from neurosarcoidosis patients are, especially the ones who are newly diagnosis, what does the future hold for me? How are things gonna go? Am I gonna get better? My life has changed a lot actually in the last couple of weeks.

[00:08:25] What does it look like? Predict that for me and neurosarcoid is fairly far behind, I think in terms of by comparison to demyelinating disorders and in terms of the level of research that has been conducted. And so, I'm trying to make myself squirm a little bit less when I get those questions in clinic. We're doing some research to try to help predict that. And that's it. Yeah.

[00:08:48] **Dr. Grace Gombolay:** Great. Thanks for telling us. And just, it just shows that there's just a lot of work that needs to be done and a lot of these rare neuro immune disorders, not just the ones that've talked about today, but there's a lot of them out there.

[00:08:57] So thank you very much. Okay. Finally, last but not least, I have a few slides that I am going to present on some of the work that we've been doing here at Emory and CHOA.

[00:09:07] And I think one of the things that I think you've noticed is that there's different types of research that can be done. So, we talked briefly about clinical trials where you are looking at a particular medication that you're interested in and then doing a rigorous study of comparing it to a different treatment, whether it's a placebo versus non-treatment or other treatments that are out there.

[00:09:29] And so that's one way of doing it. We talked a lot about different imaging type research, so MRIs oh wait, this will work. Excellent. Okay. MRIs that are out there there's a lot of retrospective research, meaning that you have data that's already collected, and you look back on what's happening versus prospective.

[00:09:46] And what prospective looks like is when you're enrolling patients and you look at things and you try to look at follow them up in future visits and see what's happening. So, this is some of the research that we're doing. So, one of the things that we've actually set up at CHOA, our Children's Healthcare Atlanta, is a prospective patient registry.

[00:10:02] And this is for all comers with all of our patients who come in with suspected neuroinflammatory disorders. So, this includes our MS, MOGAD, NMOSD, transverse myelitis, optic neuritis and other buckets. So, a lot of my patients and families are here today. You have been asked, or currently in part of this study.

[00:10:19] And so part of what we do is we collect blood and cerebral spinal fluid. We actually collect it as part of standard of care. And what that means is that if I'm doing a blood draw for clinical purposes, meaning I'm testing you for something, I'm gonna collect a few extra vials. It's not an extra poke because I think it's meant to poke kids, especially for research.

[00:10:35] Sometimes you have to, but in this case, I don't do that. And if there's any leftover cerebral spinal fluid from the lumbar puncture that was done, then I will collect that. We're actually doing some advanced MRI techniques that I'm gonna cover in the next few slides. And then I also collect clinical symptoms and then treatment data.

[00:10:50] because the idea is what treatments work best and how do we know? So, this is a recent few, couple studies that we've done. Looking at MOGAD and leptomeningeal enhancement or LME and what LME is, a particular pattern. And hopefully by this arrow that showing here, I can show you that this is what this looks like.

[00:11:07] So this is actually a brain MRI, this is what a lot of you get. And then when you get contrast, you can see certain types of contrast patterns on there. The lepto meninges are these little spaces in between

the folds of your brain. So, your brain is very wrinkly, it's very foldy. And so in between those spaces are the leptomeninges, and the arrow is showing you.

[00:11:26] Hopefully you can see here that it's bright here. This is where the contrast is coming in, whereas the folds over here is dark, so there's no leptomeningeal enhancement. Is my arrow showing up? No, it's not showing up on the screen. And where the, this white arrow on the brain MRI picture is showing there's the, in the folds there's extra white enhancement and that's leptomeningeal enhancement.

[00:11:47] And so one of the things I noticed during my fellowship and then when I was a newer full on attending physician is that I had some patients who had come in with meningo encephalitis. They looked like they had in meningitis, they had fevers, they had trouble thinking, encephalopathy. We had one patient, which is where this picture came from, who came in with an onset stroke-like symptom.

[00:12:07] She didn't actually have stroke on her MRI. People were confused, what did you have? Turns out she actually had MOGAD, they increased opening pressure. When you do the lumbar puncture, you have amount of pressure in your brain, and you can actually measure that pressure when you do the lumbar puncture.

[00:12:20] Sometimes that pressure can be high, that can lead to headaches and some, sometimes we didn't know what it was. And later on, when you start looking at the MRI and demyelination, which is white spots on the MRI, that's when people realize that you had something going on. And later on, realized it was MOGAD.

[00:12:35] There's this entity salt called cerebral cortical encephalitis, which is inflammation of the cortex, which is the outer areas of the brain. And then the Mayo Clinic coined this term called flames, which is unilateral flare lesions in MOG associated encephalitis with seizures. And one of the things that we were actually a part of with the Mayo Clinic is looking at meningitis and MOGAD.

[00:12:58] And so meningitis was identified in 34 out of 810 MAD patients, meaning that they looked like they had this infectious virus or bacteria that was affecting their brain, but it turns out it was only related to MOGAD. And so here in. Outer folds of the brain, I wish my cursor would show up on the screen.

[00:13:15] You're seeing extra signal on there that's showing that meningitis pathology. And so, one of the things we're interested is how often do you see lepto meningeal enhancement in children? And so initially we looked at, we had 21 children with MOGAD and seven out of the 21 had lemptomeningeal enhancement.

[00:13:32] And then we compared those to our children who had actually MS or aquaporin-4 N-M-O-S-D. We left out the seronegative N-M-O-S-D. Turns out 0% of the children with MS and 0% of those with aquaporin-4 N-M-O-S-D had the LME. So not everybody with MOGAD had LME, but there was a good chunk, a good section of them who had, and so now I'm wondering, can LME be a neuroimaging biomarker for MOGAD?

[00:13:56] When I look at an MRI, when a neuroradiologist who's looking at MRI, if they see the LME, I'm like now wondering, can that be a marker for MOGAD? It now gives you an earlier diagnosis. It takes a few weeks for the MOG antibodies to come back, for the test to come back. But the MRI, you get that information within a day or two.

[00:14:13] So now I'm like, oh, can this be a biomarker if it's present? And if so, what does that tell us about the biology? You have to have a certain area of inflammation in your brain to see the LME, the leptomeningeal enhancement. So, what does that telling us about the biology of MOGAD if that is different from MS.

[00:14:29] And NMO. And so, the converse, we did a different study, which Dr. Beau, who unfortunately had to leave but she was here for the panels earlier. She actually helped me look at this. So, we looked at over 900 MRI scans that had happened at CHOA over the course of two years who all had reported LME.

[00:14:46] And so we're curious, how often is LME end up being MOGAD? So, if you had a random brain MRI, how often is the Moog a d? It turns out it's 5%. Everybody else ended up being cancer related. Some sort of blood vessel anomaly related, or infection was the most common, which is what we tend to see. But 5% is actually not an insignificant amount.

[00:15:08] And so this data has not been published yet. We're putting together a manuscript and hopefully will be published soon, but to get it out there. So, if you have a patient who comes in who has LME on their MRI and you're like, oh, we ruled out an infection, we ruled out cancer. We load out blood vessel stuff, what else can it be?

[00:15:24] Hopefully now this will be out there where maybe they have MOGAD. Another thing that we looked at. This is done by Phil Sumar, who is an Emory Medical student working with me. This is also unpublished, but I was working on the paper earlier this morning before I came here. So hopefully we'll publish that soon, where he actually looked at 196 children that we now have seen at our center, including 92 MOGAD patients, 83 MS, and then 21 with aquaporin-4 and NMOSD.

[00:15:49] And the question we had is how often are we seeing seizures in children with MOGAD? And it turns out 30% of our children with MOGAD had a seizure at any, some point in during their diagnosis versus 2% of the MS and 5% of the aquaporin-4. So, you can see it's more common in, in MOGAD and it turns out going back to the leptomeningeal I enhancement, if you had leptomeningeal enhancement, that increased your odds, meaning that your likelihood of having seizures by sevenfold and this was actually significant.

[00:16:20] And so something going back to that biology, what is happening in the brain causing the inflammation that we're seeing on the MRI, it's not the leptomeningeal enhancement is causing the seizures. Whatever underlying biology that is causing the leptomeningeal enhancement is also triggering seizures. And so now I wanted to talk about some of the advanced MRI techniques we're looking at to look at blood brain barrier.

[00:16:41] And so what happens is that you have different cells in the brain that sort of protect your brain from things getting through, including infections, including your immune cells. And so, when you have inflammation in the body, it can poke holes in there. Right now, our current MRIs that you get standard are routine, can't really look at it very well.

[00:16:58] And so one of the things that we're looking at is, are there advanced techniques that we can do it? One related to that is called the glymphatic system. The glymphatic system is actually relatively newly discovered, and its cost. Thought to be the waste disposal system for the brain. We have lymph nodes.

[00:17:13] We have a lymphatic system in our body that helps drain things, including infections and things like that. The glymphatic system is also thought to be something similar, but it's in the brain. There is a type of advanced MRI technique called DTI Alps. We talk about alphabet soup today. There's a lot of things.

[00:17:29] Stands for diffusion, tensor image analysis along the perivascular space. It's an MRI technique, but it's a special MRI technique is all I'm gonna talk about with that. And so, what we've done so far, we've actually had this DTI Alps performed in 27 children with MOGAD 15 with pediatric onset MS, and then 17 pediatric controls.

[00:17:47] Data has not been published yet, but I want to show you what we found what we looked at is that, so here we're looking at the different amount. The DTI ALPS index tells you how much drainage is happening in the brain. Higher means more drainage or better filtration, quote unquote, for lack of better term.

[00:18:03] And so here in the left panel is the left side of the brain. The right panel is the right side of the brain. And then the middle panel, excuse me. And then the very right panel is gonna be the average. When we looked at the average, there wasn't a huge difference amongst the groups or the right, but when you look at the left, you can see here that MOGAD had a lower DTI Alps compared to our healthy controls.

[00:18:26] And the MS, so there's something about MOGAD that there's not, the brain is not draining as well as compared to MS or other controls. Again, I don't have any functional data. What does that mean for patients functionally? And ultimately that's the important piece of this, but that's the next step that we're gonna do.

[00:18:42] Is that, is can we look at these DTI Alps? How does that relate to function? And can this be a better test? Because I think what can be frustrating for patients and families and for us is that I have a patient comes in with a symptom, is a symptom related to a relapse or a flare up of their disease.

[00:18:57] But the MRI looks okay, so what does that mean? What does that mean? And so that's one of the things with these advanced techniques, can we get a better look at the system? Can it get us a better sense of, oh no, even though this part of the MRI looks okay, we're seeing your DTI Alps has changed.

[00:19:11] And so what does that mean? Does that mean you need different treatment? What's going on? So future work that we're doing includes looking at ai, AI is everywhere. It's in our phones, it's everywhere. And so, is there AI that can help with an earlier diagnosis? We're actually having, using AI to look at all of our MRI images, can they give you an earlier diagnosis of MOGAD versus MS versus N-M-O-S-D, so you're not having to wait weeks or months between for the results.

[00:19:38] One of the other things that I'm putting together with a few folks, including from Australia and from Mayo, is an international treatment consensus guidelines for MOGAD because one of the things that you've noticed is that each doctor will do their own thing based on their experience of what they think that is best based on what we have.

[00:19:55] We don't have the treatment data quite yet, but it's coming down the pipeline. And what we're doing is that we're getting a group of experts together, about 30 experts around the world to come together to put together consensus guidelines. Not only for places that are more resource rich but also resource poor regions.

[00:20:13] What are the options for them if they're not able to have access to the same thing we do. And finally, this is I think also a really important question that goes back to our biorepository that we are doing. Collecting blood and things like that is what I would love to do is predictive markers.

[00:20:27] Is there a blood test I can do that's gonna predict whether or not you're gonna have a relapse? If so, when is that relapse gonna happen? Is there a blood test I can do to pick out which treatment is best for you? Right now, we have lots of good treatments that are available for these diseases but it's a trial and error.

[00:20:43] We're like, okay, we're gonna try this and hopefully it works. And if it doesn't work, then we try something else. But what I would love to do is say you have this protein in your blood, that means you're gonna respond to this treatment or you have this protein in your blood, that means you're gonna respond to the other treatment. That's the goals for our future work. And with that we'll take any questions you guys have

[00:21:04] **Audience Member:** So, you were talking about looking at the sun in the morning and thereby setting your sleep wake cycle. I heard the theory enunciated that the glymphatic drainage only happens in deep sleep.

[00:21:28] **Dr. Grace Gombolay:** That is a great question. We're still learning about the glymphatic system and what it does and its role in, not only in neuroinflammation, but aging, for example. They're looking at it in things like Alzheimer's and dementia and other things. Emphasizes the role of sleep. The thought is the glymphatic system.

[00:21:47] That's one of the roles for sleep. because we actually we know that we need sleep, but what are the underlying biology processes that are happening during sleep? And we actually don't know that, but that's one of the things. So, thank you for bringing that up.

[00:22:01] **Audience Member:** This isn't really a question but more so an opportunity to thank you all for the physicians and the doctors and the teams for studying and doing research and answering all our questions because not that doctors need to be incentivized to do things, but these diseases are super rare.

[00:22:22] And though they don't impact numbers on paper, large numbers on paper, like I'm sure each and every one of us is super grateful and thankful that you guys are doing this kind of work. So, I really appreciate it.

[00:22:39] **Dr. Grace Gombolay:** Thank you for that comment. I will be honest, I'm a nerd. This is really fun for me, which is why I do this work. But it's really meaningful to hear, so thank you. Any questions, comments?

[00:22:55] **Audience Member:** My question is regarding like how you choose what to study and where to focus your research, especially like the journey toward like actually putting a name to a cluster of symptoms that patients are presenting with. Like prior to having a name for MOGAD, there was patients that were still experiencing that, but there was probably not a definitive diagnosis for that.

[00:23:20] Like what does that journey look like for diseases that have yet to have a formal name put to it? Or from a professional perspective and from a personal perspective, I see a lot of patients that have I'm about to say the word pants and pandas that have to seek treatment outside of traditional medical facilities.

[00:23:43] And then like how we move that kind of research forward to continue that work where, you know, diseases that don't yet have a, an accepted name or diagnosis can eventually be so.

[00:24:02] **Dr. Grace Gombolay:** So, what's really challenging now, especially in this financial landscape, is that funding places are getting far and through between including, I'm not gonna talk about politics right now, but when there's limited funding, then unfortunately our research is gonna suffer on the bright side about that.

[00:24:19] For example, the NIH does have such funding mechanisms including for rare disease clinical research because they understand the need for that. And actually, we were recently received one of those grants to look at autoimmune encephalitis. So related to MOGAD but a separate entity.

[00:24:37] But there's so much overlap between these diseases as you all are aware. And so, the idea for this autoimmune encephalitis registry is that we take all comers that fit certain criteria that look like they, if they could be autoimmune encephalitis or not, and then collect their data, collect their blood, collect their spinal fluid, collect all the information we can.

[00:24:56] And the idea is to start having better diagnoses and start parsing out, okay, you have a whole bunch of people who look certain, a certain way, but what is that? I liken this to autism because I think a lot

of people are familiar with autism. Autism is a huge spectrum of symptoms. You can have multiple people who are diagnosed with autism, they look very different.

[00:25:16] And I think one of the reasons why we don't really know the cause of autism is my suspicion is that there's different causes for each person. We're just seeing the end point of it. And then how do you start parsing out, okay, this person, it is related to inflammation, for example, which is where that pans and panda comes in, is that the thought is their symptoms are related to inflammation versus there's some genetic, there's some chemical imbalance in the body.

[00:25:39] And so I think we have to start lumping, separating, lumping again as much as possible. But we need funding. So as part of advocacy, if you can, and I'm gonna be selfish about this, if you can talk to your congress people, all of this stuff to really advocate for funding for rare diseases. because my worry is that they're cutting funding for a lot of things and that unfortunately our science and research is gonna suffer as a result.

[00:26:04] So I'm off my political soapbox.

[00:26:07] **Audience Member:** How, much do you rely on the patients themselves and for, your research and does what best informs your research? Is it survey data? Is it patient experience from the people that visit your clinic? Is it blood draw? What, how can patients get involved and what's the best way and that advocacy organizations can help?

[00:26:33] **Dr. Grace Gombolay:** Yeah. There are multiple questions loaded in there. I think first of all is that I'm constantly learning from my patients and families. If I have one, if I have multiple patients and families, they're like, oh, I've seen this, or this is happening. That triggers in my mind, oh, has anyone looked at this?

[00:26:51] Oh, no. Then we should start doing that. That's why survey data can be really helpful, really meaningful. There's been a lot of meaningful studies that have come out of survey data and then being involved with groups. because these are rare diseases and the only that we're gonna learn from it and learn from each other is by coming together.

[00:27:08] And that's one of the ways that these advocacy organizations, these patient organizations can come together is to help bring us all together. There is one more part of your question, Julie, that I just missed. Yeah.

[00:27:22] yeah. So, the question is what, which part of the research which part of this lens affects my research the most? I have, I say all of it, which I know is probably not the most satisfying answer, but I think all of its important, right? Patients and families come with questions of their own.

[00:27:37] And that's actually one of the things I really appreciate about the Rare Disease Grant through the NIH is that you're required to work with patient advocacy organizations. They have to be part of the steering committee. They're part of the research topics and things that are happening. And so, because of that one of the things that we're looking at is outcomes and quality of life.

[00:27:58] because surprisingly there has not been as much quality-of-life work, especially in the autoimmune encephalitis space. And so that was something that our patients and families and caregivers came to us and they're like, we need to look at this. And that's, part of what we're gonna look at.

[00:28:14] I think we're gonna end it here today. Thank you so much for coming. I know this was a long day. Thank you so much to SRNA, to all the people who have supported this effort.