

# Cognition, depression, and rare neuroimmune disorders

You can view this presentation at: [youtu.be/hQGUyFU1eF0](https://youtu.be/hQGUyFU1eF0)

[00:00:03] **Dr. Lana Harder:** Thanks so much for having me. As we get started, I just wanted to share a few acknowledgements. First and foremost, those patients and families impacted by rare diseases who teach us everything we know about that and allow us to advance science in this area. And I also want to thank SRNA for bringing us all together as a community for events just like this one. I also really appreciate participating for many years in the Family Camp as well. It's a wonderful community where we get to share what we're learning about these conditions. And I'm very thankful to be a part of it.

[00:00:42] I also want to acknowledge my team in Dallas who have the privilege of serving our patients with each and every Friday at Children's. And they are also the reason that I've had the chance to learn so much about these conditions. So just wanted to get started by mentioning a little about our clinic and letting you all know I am the neuropsychologist that has had the privilege to be a founding member of our clinic serving kids with rare CNS demyelinating disorders. And we opened that clinic back in 2009. So we've been at this for a long time and have managed to have a lot of fun and meet a lot of really wonderful patients and families.

[00:01:29] These are the CNS demyelinating disorders that we work with in our program. So multiple sclerosis, ADEM, NMO, optic neuritis, transverse myelitis. Today, I'll be focusing more on - well, actually, I'll be touching on all of these, but with a focus on learning about these rare neuroimmune conditions. So for those of you who may not have encountered a neuropsychologist before we're very focused on the science of human behavior as it relates to the central nervous functioning. And we really look a lot at cognition. We're known for testing things like attention and memory. And a whole host of things I'll talk about today, but we also look at behavior, emotional functioning quality of life, experience of fatigue, and how all of this really goes together to underlie how we show up each day in our daily lives.

[00:02:31] And within that, we really want to understand how a medical problem may show up or how it may impact a person each day. My roles are in clinical care. As I've mentioned, also research which I'll be talking about today. And then throughout all of our work, we seek to educate others, the next generation of clinicians coming through. And I've had the chance to participate in leadership as the co-director of our program. Neuropsychological evaluations, as I mentioned, really focus on assessment of those cognitive functions. So a lot of standardized tests and this is one-on-one much like the pictures show here. We have

folks who train in adult-focused neuropsychology, those like me and pediatric neuropsychology, and even those who really cover the lifespan.

[00:03:20] Our goal is to understand how a person's functioning relates to others, their age to see about where they are. And I'll talk about that more as we describe some of our research and the things we've been learning. I always like to acknowledge the different roles, roles as clinician and researcher. And we often put those together, especially when we're sharing with patient families what we've been learning in our clinical practice. So that's a very exciting thing to really feedback that information we've learned to our patients and to share the latest that we know. As a clinician, though I'm focused on one individual and really understanding how a medical problem impacts daily life, as we said before, from that, I create a tailored plan and intervention for them.

[00:04:14] In research, we're really looking at the group level to try to understand a given diagnostic group. We might focus in on an age range. For me, that tends to be zero to early adulthood, age range. And we have focused in on transverse myelitis or MOGAD things we'll talk about today. So it depends on the study and what we're trying to find out. But the focus is different depending on if I'm wearing that clinician or researcher hat.

[00:04:51] So I wanted to share a little bit about our research journey and I'm really going to try to hit the high points here and allow time for some Q&A. I'd love to hear from our participants and talk through anything if you have questions about what I've talked about today. In the beginning, we really were interested in comparing two groups, one multiple sclerosis with known brain involvement. And then we wanted to compare that with transverse myelitis where we don't see clear brain involvement. This is a condition that impacts the spinal cord.

[00:05:21] So in an early study, we hypothesized that those with MS would have more difficulty with cognitive function and school problems. And so our aim was really to compare the groups to show that. While we did see some significant cognitive problems in MS that we did not see in TM, we saw independently cognitive problems in individuals with transverse myelitis. And what really struck me as a pediatric provider was that these groups had an equivalent rate of school problems, which was an indicator that there was some difficulty going on there. And we published this work and showed the frequency. So how many in our sample as you can see in the percentages showed problems with a given domain like memory or attention.

[00:06:12] Again, this was more than we would have expected for a condition that impacted the spinal cord only. From this, we noticed that many of those showing problems with cognition also had high rates of fatigue and that was noteworthy to us. So we started to wonder if fatigue is playing a role. We also wondered if depression could impact cognition much like we would see in other studies of other populations. So we wanted to carry this work forward, but we did so with a little bit different lens. So instead of the comparison that we made going in where we were really looking at transverse myelitis as a control group to further study MS, we're now flipping this around and thinking of MS as a control group for rare disease research. The reason for that being that we have more knowledge of MS and how it impacts our patients. And if we could compare a group of individuals with MS to some of these other conditions, it would really help advance our understanding.

[00:07:22] So with that context, I want to mention some of the things we do know about MS. And again, I'll try to hit some high levels here. When it comes to fatigue, this is one of the most common symptoms in MS. It's also known as the most debilitating symptom of MS in many cases, we know that it impacts quality of life. With depression, we know there are high rates of clinical depression in individuals with MS. There's been a lot of discussion and study of that role of inflammation as a biological basis for depression. Also when it

comes to cognitive functions, about a half of adults with MS will have cognitive deficits and about a third of our pediatric patients have this experience. So we do have a pretty good foundation and framework for understanding how MS shows up in these domains.

[00:08:19] And certainly our understanding is far more advanced than what we know about our rare conditions that we're focused on today. So some of the previous researchers out there had looked at adult MS versus NMO and really saw that there were no differences between NMO and MS when they gave some cognitive tasks. And that was really striking to me as an early researcher, really trying to understand these conditions, everything I read at the time said that there was really not expectation of brain-based symptoms for NMO for instance. So I want to highlight this great work that was done. That's along the lines of what we have done to try to further advance our understanding. So going back to some of these questions, what role is fatigue playing? What about symptoms of depression? And this became the topic of a dissertation.

[00:09:20] And I really want to give a shout-out to my former dissertation student, Dr. Cole Hague, who has recently started a position at Children's National in DC where he is actually seeing patients with the conditions we're talking about today. He had a lot of training in that area when he was with us in Dallas. And as you can see, did his dissertation in this area. So I do want to mention for those who might travel up that way or live in that area, he is just starting to see patients there now.

[00:09:51] So with his study, he wanted to compare fatigue and depression again in these groups of MS compared to TM. And to really explore that relationship of fatigue and depression as it related to a person's cognitive status. It's a very busy slide. The high points are he had 67 with MS, 53 with transverse myelitis and looked at a cognitive screening battery as well as some questionnaires related to depression related to quality of life and really focused in on quality of life as it relates to fatigue. So what he found - and this was a really big finding for us as a clinical team serving kids with MS and TM, what we saw were no differences between MS and TM when it came to fatigue.

[00:10:46] And as I mentioned in an earlier slide, this is striking because we understand that fatigue is a very prominent feature of MS. So when we can say we don't see differences between MS and TM, that's pretty significant and actually, very validating. I think in my work with TM, where we would talk about fatigue a lot, fatigue was a focus of the recommendations we were making on an individual level to help folks with daily functioning. We also did a comparison to what we would expect based on the normative data that we had and we saw statistically significant worse fatigue in both groups across all areas.

[00:11:34] So moving along here, I want to talk about depression symptoms and I should clarify. These were not diagnostic interviews that we did as part of this study. These are really just symptoms of depression that we were measuring. And we saw no differences between groups when it came to those symptoms of depression. You can see the rates here, about 25% with MS were elevated, and 27% with TM. But then we also saw no difference from the normative mean. So no difference from what we would expect, generally. I always want to point this out because this comes up among our providers and our patient families, we talk a lot about the overlapping symptoms of depression and fatigue and how can you tell what's really going on?

[00:12:29] So the symptoms that they have in common would be changes in sleep, motor, slowing, loss of energy, diminished engagement and activity, and even diminished cognitive skills, like being able to focus. But then, we can separate these out and we can think about what would make these distinct areas. So really with fatigue, it's simple. It's about feeling tired and how that leads to reduced engagement in activities, even feeling physical symptoms of feeling weak. With depression or symptoms of depression, this is more of a

depressed mood, a low mood, feeling sad, empty, hopeless, changes in weight, motor agitation, feelings of worthlessness, guilt, and then recurrent thoughts of death and dying can all be part of a clinical depression or symptoms of depression.

[00:13:27] And you don't have to have all of these. It's just some symptoms that we really want to think about and look at when we're trying to differentiate what's going on here since we know that fatigue and/or depression can be these common symptoms that we see. And then when it came to cognitive impairment, what you see here and maybe as we might expect, more individuals with MS met criteria for cognitive impairment. So 42% compared to 21% of those with transverse myelitis. What was really interesting to see when we looked at this sample as a whole, that those with cognitive impairment were more likely to have elevated general fatigue. So we saw some association there with cognitive impairment and fatigue.

[00:14:20] Then we asked - this was the last analysis of this dissertation, what factors predict cognitive status in MS and TM? And so all of these variables were entered into a model to see what was predictive. And the one thing that was significant in our analysis was depression. So that greater symptoms of depression increase the likelihood of a person's cognitive impairment in this study. So again, creating those links with fatigue and with depression and cognition.

[00:14:56] One thing I think is really important to note here is we see all of these things come together and overlap to create a challenge in daily life. And when we have studied these things in other populations, there is evidence that by treating one problem, you may also be treating another. And I think that that's a really important takeaway from this conversation today. Is, really how do we prioritize the one thing or one or two things that are making things more challenging? And then to have this awareness that when we improve one thing, we might see that we improve in other areas.

[00:15:39] So I want to switch gears and I know this is just 30 minutes we have together. So you'll see, I'm packing in a lot here. But one thing that has been really exciting coming out of our program is the learning that we're doing about MOGAD. So this is one of the newer conditions that we've been learning about and studying. I'd say an exciting part of this field is just the new discoveries all the time and the research and how we put our heads together. We have our physicians and neuropsychology and a whole host of other specialists, really smart people that have taught me so much and when we put all of this together, it's really great to just see what we can learn and how we can advance the understanding. Because if we do that, it gives us clues about how we might help and be more helpful to the patients that we serve.

[00:16:137] So MOG is a glycoprotein important in the myelination of nerves in the CNS. And the most common demyelinating syndrome associated with this anti MOG antibody is ADEM. And that actually shows up in our data as well. MOGAD is more common in pediatric patients and I'd like to share with you what we've been learning again in our clinic. So here, I've captured the clinical presentations, the conditions that we see associated with MOGAD. Little is known about the neuropsychological outcomes. Again, this is a relatively newer area for us. And so we took a look at our data on our MOGAD patients. So this is a retrospective of looking back at the data we had, which was for 45 individuals ages five to 19.

[00:17:33] And again, most of these had ADEM, I want to mention which is what we're seeing broadly. Also, that was followed by bilateral optic neuritis. Then optic neuritis at 11% transverse myelitis and then our optic neuritis plus transverse myelitis. We gave the screening battery. This battery was designed thinking about areas that might be vulnerable in the setting of a demyelinating disorder. So processing speed, fine motor skills, aspects of memory learning and attention other things like that. So just to tell you how we approach this. Earlier I mentioned that when we are testing an individual, we're trying to understand how their functioning looks compared to others, typically, it's others their age, that's how measures are typically created.

[00:18:31] So if you can see in the green area here, about 68% of individuals will fall in this broadly average range. And we had to draw a line at the low end of that. So looking at or below this typical range that we would expect for a person's age. And we looked at how often someone's score fell at that point at or below that range where the line was drawn. I will tell you that as a group when we pulled all that data together, and we looked at an average score by test for this whole group of MOGAD patients, most fell in the average range, most of those scores were average. But there was a lot of variability which is why we chose to show percentages of those falling below where we would expect them to be.

[00:19:26] And just broadly, more than 30% show difficulties with the hands-on fine motor coordination. More than 30% having difficulties with verbal learning and memory and then those that same number with problems simple and complex attention. I put an asterisk by that because the test that we use were hands-on fine motor tasks. So you have to keep that in mind if fine motor is already a weakness. But we're asking people to do things with their - in a hands on way, we want to be mindful of that and that that could be driving the difficulties that we saw. And then greater than 20% had difficulty. So visual motor integration is just paper-pencil coordination. These were untimed though tasks. So auditory attention, working memory, which we think of as a mental scratch pad, holding on to information and using it to do something else.

[00:20:27] Processing speed again, a fine motor task there, so I wanted to denote that. And then verbal fluency, how quickly they could generate a verbal information when prompted. And then about half that sample was receiving educational support services. So I get another signal that there are some challenges in that learning environment. So in a big picture, summary, individuals with CNS demyelinating disorders are considered to be at risk in the areas that we spoke about today. But it's really important to point out that not all are affected. And as I said, those outcomes really vary widely. Something I don't have on this side that I should say is that there can also be variability, day-to-day or hour-to-hour.

[00:21:18] So if someone has a problem on my testing, that's just a snapshot in time. That doesn't mean that that's constantly or always the situation for them. We know there's no one-size-fits-all approach just because these disorders are so different and again, the outcomes are so variable. But we believe that the research we have and that we're growing really offers clues about these targets for intervention. I want to give you a great example. I mentioned on this slide that verbal in memory is a problem. But I didn't really describe very much about the task that we were doing. What we saw is that individuals were given a list of items to remember over five trials, the first trial, they had a lot of trouble remembering what was on the list.

00:22:07] But after that, with repetition, everything went normalized, went to what we would expect. So this is looking at them as a group. So that tells us that repetition rehearsal, here are some examples here and I have that in the orange box. If we give some repetition in rehearsal, studying, looking at information more than once when trying to learn it, is a simple thing that can help address that. It just tells us it might take a little bit more exposure to the information to get in there. I want to also say there are many opportunities for intervention, there's a lot we can do and we want to tailor those things to meet individual needs.

[00:22:53] So again, here are some examples. This is more geared for academic environment which being a pediatric specialist. And even working with folks in the college environment, these are things that we talk about a lot to address the difficulties or weaknesses that we might be seeing on testing. And we also want to take a strength based approach. So when we look at an individual on testing, because we're human, everyone has things that they're better at and things that are harder for them. So we really want to leverage those strengths to address areas that are more difficult, so we can be strategic. So things like reduced distraction environment sitting near, in the front row to block out distractions, assistance with note taking. So we can better focus in on the lecture.

[00:23:47] So getting copies of notes, extended time for exams is a big one that can really help our patients. And then just so many other things that really support us day to day for all people to think about. And I think when we talk about these rare conditions and some of the associated features, the fatigue, we know that sleep is important for human beings. It's an important thing. And so making sure for our patients with these conditions where we know fatigue is already a factor or at least, is a risk. We really want to make sure we're prioritizing good sleep.

[00:24:32] Things like exercise, you see my picture of these beautiful leaves and time in nature. There's some emerging research about that and how that can promote wellness. Considering a period of individual therapy, if we're addressing symptoms of anxiety or depression or other things that are going on. Building community, I think being here and part of a program like this tapping into resources with others who maybe share in common a medical condition or a range of medical conditions can be a really powerful thing. And we see that in these events and in our family camp.

[00:25:17] So I want to mention that, I think there can be and there is times of shortage depending on where people are of mental health professionals. But the accessibility is something that our field has been working on through virtual services and that's depicted in one of these here. So I could go on and on about all of these things that can serve to support people in daily life. But I really want to pause. I'm looking at the time. I want to make sure we have a few minutes for some questions. But thank you so much for listening and I look forward to hearing from the audience.

[00:26:00] **Moderator:** Thank you Dr. Harder for this very helpful information. We do have a couple of minutes for questions and one came in. It reads, "Once deficits and cognition are documented, who can best advise and provide rehab services? Do we know which aspects are most likely to respond to intervention? And how can families know what to expect for long-term outcomes and functioning, such as severe processing speed, attention, memory, fine motor skills, looking toward high school and beyond for launching into adulthood?"

[00:26:41] **Dr. Lana Harder:** Yeah, such an excellent question. So there are many - and I want to say, I think this question really also highlights the importance of individual assessment to then tailor that treatment plan. So a neuropsychologist or someone that provides assessment services would be able to really detail. And so it sounds like as a question asked, once deficits and cognition are documented, with that should come a list of recommendations to help strategize and prioritize where to start on all of that. There are fabulous providers in rehab settings.

[00:27:20] We actually have a neuropsychologist in our rehab program as well as our speech-language therapists or OTs, PTs, all of those great providers that provide all kinds of rehab services. And it can be really important to work across more of the physical and the cognitive. And there can be like a synergistic effect when we tackle those things if that's relevant for an individual. As far as what aspects are most likely to respond to intervention, I would say this is an area that is less developed for us. I think we're really good at documenting or describing at a group level, the problems. And it's really important and I think for our field and focus here to really turn the quarter and start to talk about or look at what are those interventions. And what are the outcomes of those like? What would be the most effective? So it's hard to say for sure.

[00:28:21] The other factors to consider have to do with time since onset or injury if we think about insult to the brain as a very broad thing, but if there have been lesions to the brain, when did that happen? Are we within, months, years after? We do believe that people can continue to heal over a very long period of time. And we're really wanting to focus in that first year to two years on getting the most we can out of that window when the brain is in the central nervous system maybe are actively healing. So I know that's an important

window. It doesn't mean that all progress stops at that point, not at all. And the other point I want to make is there's that remediation that we're talking about rehab, like bringing those skills back, remediating skills.

[00:29:18] Then there's accommodation. So we really think about as time goes on and see where we are. And what functioning is like across multiple areas. We also want to be thoughtful and strategic about accommodating. So I had mentioned things like extra time for tests or note-taking assistance, things that would not change the work that a person is doing if they're able to do it at the same grade level as their peers. But gives them a chance to show what they know again through something like extra time.

[00:29:57] So I think the last point to make is a re-evaluation is really important to check and see how those rehab efforts are going. And to continue to think in terms of remediation rehab and also accommodating to allow a person to maximize their participation as they continue to work on those skills.