The CNS Connection and Psychosocial Aspects of Being Diagnosed with ADEM, AFM, MOGAD, NMOSD, ON, or TM

You can view this presentation at: youtu.be/fPTyf1jzDw8

[00:00:00] **Roberta Pesce:** I am honored to be joined by Dr. Lana Harder, pediatric neuropsychologist at Children's Medical Center of Dallas, and associate professor with joint faculty appointments in psychiatry and neurology at the University of Texas Southwestern Medical Center, to talk about the CNS connection and psychosocial aspects of being diagnosed with rare neuroimmune disorders. Hi, Dr. Harder. Welcome, and over to you.

[00:00:33] **Dr. Lana Harder:** Great to be here. Thank you so much. This is one of my absolute favorite topics. So, I was thrilled to receive this invitation, and we'll spend some time over the next half hour or so talking about the relationship between these medical, complex medical problems and how that might manifest itself in daily life. Knowing that it's very complex, it's a complex picture, there are so many factors that go in to how we show up each day in our lives. So, I'm going to see if I can advance my slides here. Alright.

[00:01:11] I want to start out by acknowledging the patients and families impacted by rare diseases. It is such an incredible two-way street that we have between myself as a clinician and educator and getting to present at events like this, but also thinking about how so much of what I know I have learned directly from those I have the privilege of working with, both at Children's in Dallas and UT Southwestern. But also, when I attend events like this one, through SRNA, as well as the family camp, when I participate in podcasts and get your really fantastic questions. So, there's just so many, such a richness that I get out of these interactions, and a lot of this then informs my work as a clinician and also as a researcher. So, it seemed appropriate to start just with this acknowledgment right off the bat.

[00:02:09] I also have to acknowledge and want to acknowledge my fantastic team in Dallas. We're so fortunate that we get to come together each Friday to serve the patients who come to our specialty clinic that is focused on these rare disorders. And so, I just wanted to give a shout-out, I really am a big believer in multidisciplinary care, and that we can do so much for our patients and families when we are all in the same room putting our heads together to see what is best for that patient, as well as the excellent collaborations that we have for our research as well, and I'll get to talk about a lot of that today. So, I know that this would be a review for many in this audience, but I did want to touch on the role of neuropsychology so all of you know the lens that I use.

[00:03:00] So, I am not a medical doctor, that's usually a huge relief to the patients when they walk in our clinic rooms. I am a neuropsychologist, and this area is focused on the science of human behavior as it relates to central nervous system function. And then beyond that, the focus that I have is demyelinating disorders. So, when there is something, a disorder that impacts the CNS, I'm looking at how that shows up for the person in terms of cognitive skills, and you've seen many examples of that such as memory and attention. But also, behaviors and emotions, fatigue, all of these things come together to impact a person, and so we try to tease these things apart and look at these in our evaluations, and I'll talk more about that.

[00:03:52] At the individual level, when I have an evaluation, when I have someone that comes to see me, I'm looking at, again, how a medical problem, and this is an MRI showing lesions in the brain and spinal cord, how is that showing up for this teen in the classroom, who's expected to go to school and learn each day? What does that look like for her? But also considering a whole host of other things, so we know that the medical event or the medical problem is simply one piece of the overall picture. We know, for instance, there are individuals who, with or without a medical problem, may have been at risk for dyslexia based on family history or an attention deficit disorder, something like that.

[00:04:37] But a person brings a lot of other things to the table genetically in terms of their developmental history. It's important that we look at the developmental trajectory and consider when an event or medical problem started, is it one that will continue? Or was it a one-time thing? But then if it was a one-time event, what residual changes are there that we need to consider and plan for going forward. I also spend a lot of time talking about family and school, what the support and resources are like in this person's environment We talk a lot about emotional functioning and coping. So, there are just so many different things that we're looking at when we're evaluating an individual in a clinical setting. And so, I wanted to acknowledge the difference in my clinical evaluation process where I'm focused on that one person, I'm tailoring each and every step of the evaluation to that individual, as well as the treatment plan. The plan that they leave with is tailored completely to them.

[00:05:42] When we talk about research, we're really looking at groups of people, generally. So often this is a diagnostic group, so we might say we want to learn more about individuals with ADEM, so we're going to take a lot of kids, let's say ages 5 to 18 and we're going to evaluate them and put all this data in the database, and really look for patterns and for trends. And typically, we have some educated guesses at the beginning of those projects or hypotheses that we get to test. We analyze that data, and we get some answers to our questions, and this is happening at the group level. The reason I want to acknowledge this is I'm going to talk a lot today about some of our research findings, but I want to acknowledge, as was said in the last presentation, one size does not fit all. So, if I share something about what we have learned about group X, whoever that group might be, that doesn't mean that that is going to be true for every person in that group. So, I want to say that as we think about the research findings that we have had, and we'll discuss today.

[00:06:49] So, one way I like to approach this is to really just tell you a story about how we progressed in our research journey. This is going back to 2009, it's been a really long time. I just celebrated 13 years at Children's and UT Southwestern, and most of that time I have been focused on these conditions. And initially we were, I was straight out of fellowship. I was very intrigued by and interested in our patient groups, particularly those with brain-based problems and I'll use multiple sclerosis as an example, where we could see that on imaging. One of our neurologists said, "What if we were to compare our patients who have these brain lesions that we see over time, we see it's a chronic or recurrent problem, and let's compare them to a patient group, transverse myelitis, where we don't see lesions in the brain, that would be just a great control group, and we could really learn a lot about MS when we compare to our group transverse myelitis.

[00:07:57] So, we had some unexpected findings and it's, I think, really exciting how research, a research journey can really shape the focus of our work over time. So, we did exactly what I said before, we wanted to compare MS and TM, and we were hypothesizing that those patients with MS would have more difficulty as it related to cognition and school problems. And what surprised us was that we saw, while there were some differences seen, as we expected in MS and TM, with MS having a bit more difficulty, we also saw some cognitive difficulties in our group with transverse myelitis. And then what was surprising was the equivalent rate of school problems, so saw school problems in about a third. We ended up switching gears entirely, instead of publishing the MS compared to TM paper, we really just focused in on transverse myelitis. And, I'm just sharing some of the highlights from that.

[00:09:01] We just really described what we saw in this cohort of children with transverse myelitis, just seeing higher than expected cognitive difficulties in memory, attention, and so forth. And what we also gathered from this research was parent report, the attention problems, and some depression symptoms, but again that school difficulty was about 1/3 of the group. High rates of fatigue were also noted. So, while we didn't run a bunch of fancy analyses because we didn't have the sample size to do that, we did qualitatively look at those having trouble with cognitive functions and saw a high rate of reported fatigue. So, we were left with a number of questions. I could make a list much longer than this about my research questions right now. For the purposes of this talk we only have a short time, so I'm going to talk a little bit about what we've learned in this realm.

[00:10:01] So, we continue to wonder, and at that time and going forward, about differences for our patients with multiple sclerosis and transverse myelitis for both groups we're curious what role does fatigue play? It can certainly play a role. And how about depression? We all know mood can impact cognition and that's actually in the literature. We see that quite a bit. So, and I'll talk about that more. So, we started to think of multiple sclerosis as a control group and learning more about our rare diseases. What I think is extremely exciting about the MS literature is that when we address an area of difficulty, right, so cognition, mood, fatigue, these are all interrelated. This is a big takeaway point from today I want all of us to really appreciate, these are inter-related things and when we treat one of those things, we may be treating another. So, we'll talk about that more, but it's this thought that we may be getting a bigger bang for our buck than we even realized when we, for instance, address depression through therapy and/or medication, or something like that.

[00:11:21] We may then also see improvements in cognition, for example. So, just a couple of quick examples about how other researchers have compared MS to some of our other groups. This is actually adult-focused research on neuromyelitis optica, and I won't go through each of these studies, but some things that have been really notable and interesting to me as a researcher in this area, are that when they compared these two groups, they saw, they did not see significant differences in cognition for those with multiple sclerosis and those for neuromyelitis optica, which was pretty eye-opening for me in thinking about the previous literature before these studies that had really talked about relative sparing of the brain. This doesn't mean that we know for sure the exact brain mechanisms or the mechanisms underlining cognition. There are some studies that are looking into this more, but again we go back to how do all these other factors that I've talked about really show up and impact something like cognition?

[00:12:37] In our pediatric world, we are aware of some studies where they've compared multiple sclerosis with ADEM, and so there's a study, a very small cohort, but really one of the only studies that we have in this area. This study found that those with multiple sclerosis had more difficulty across cognitive domains. And, while our, the patients with ADEM in this study showed pretty normal levels in many cognitive areas, there was a weakness that was noted in complex processing, so that was an interesting finding. And the thought

was that because multiple sclerosis is a chronic disorder that we see over time, there may be more difficult or more difficulties over time, worse outcomes. I think though as we learn more about ADEM and anti-MOG and realize that we may see events recur over time, this is something that we need to be thinking about more is basically the chronic diseases and how that shows up. We do have some work under way on anti-MOG right now, and hope by the time we meet again we have more to tell you about that.

[00:13:57] So, one of my fabulous dissertation students, he is done now, as you can see by the PhD, Dr. Cole Hague, who just finished a fellowship relatively recently at Boston Children's and has gone over to Mass General. He did his study on this very topic, so extending the work that we had done on our team, he wanted to really understand the role of fatigue, depression, and other clinical factors in determining cognition, again looking at MS and transverse myelitis. So, to set the stage for that, I think it's really important to acknowledge what we do know about MS, and this is a literature that is more developed than the literature we have in our rare neuroimmune conditions, which is why comparing these groups is actually, I find, very helpful to do because we do know so much more about MS.

[00:14:51] So, just to kind of set the stage here, fatigue is one of the most commonly reported and considered the most debilitating symptom of MS. It impacts quality of life and can impact many or most individuals with MS. We see that in adults and pediatrics. And in terms of depression, we see a lifetime rate of depression for those with MS at 50 percent, which is quite high. There is a lot of discussion in the literature, the role of inflammation as the biological basis for depression. And then as we've studied pediatric MS, about half of patients who had onset of their condition in childhood meet criteria for a psychiatric diagnosis that may include depression, but also others.

[00:15:46] And then just briefly on MS and cognition, it's pretty well established that about half of adults with MS will have cognitive difficulties and about one-third of our pediatric patients with MS may experience cognitive dysfunction, so we've seen this replicated across time in the literature. So, Dr. Hague's dissertation project was to evaluate and compare fatigue and depression for groups of pediatric patients with MS and TM, and then to look at the relationship of those factors as it related to cognitive status. And so, this was the largest sample we had evaluated and studied at the time that this was, the study was done. So, 67 patients with multiple sclerosis, 53 with transverse myelitis, you can see the average age is a little bit different with MS. Average age 15, being a little bit older than a mean age of 12 for transverse myelitis.

[00:16:52] So for this study, the participants completed a cognitive screening battery, and then caregivers and patients completed a number of questionnaires really looking at depression and fatigue. So, I want to tell you a little bit about what Dr. Hague and all of us found in this study. I would say this was one of the most eye-opening results that we had in this study, and this was the first study that we were aware of, that showed no differences between MS and TM when it came to fatigue. So, what we're saying is we know that individuals with MS have high rates of fatigue, this is a debilitating symptom of MS that is endorsed across the lifespan for those with MS, and we actually didn't see a difference when we compared to transverse myelitis, and in a way this kind of validates the experience for those with TM in that it says there are no differences, and we already know fatigue is a problem for MS.

[00:18:03] The other thing we wanted to do, which is another way to look at the data, was to compare to what we would expect in a normal population. So, both groups, MS, and TM, had significantly worse fatigue across areas when we compared just to the norm that we had. So, a really big finding for this study here. And here you can just see the rates of problems with fatigue, and you can kind of look at this qualitatively and look at the numbers to see with general fatigue those rates are almost identical. But when you get in to sleep fatigue and cognitive fatigue, there are some differences there, again on a qualitative level with less symptoms in transverse myelitis compared to MS. But still, when we ran those statistical analyses, we saw

no significant difference there. And then in terms of our depression symptoms, we also saw no differences between the groups. And again, knowing that depression may be a pretty common symptom in MS, this was noteworthy as well.

[00:19:18] But when we looked at differences for the norm for each of the groups, MS and TM, there were no differences, and you're going to see here these rates. And just to clarify, these rates are not for a clinical depression diagnosis, but symptoms of depression, so I want to make that really clear. So, it's roughly a quarter in each group were endorsing, or the parent, rather, was endorsing symptoms of depression for their child. So, I wanted you to see that data there. Something that is extraordinarily difficult for us to tease apart is symptoms of depression and fatigue. So, we know that there are overlapping symptoms. So, this is a subject of discussion among my physician colleagues, my psychologist colleagues.

[00:20:12] We talk about this a lot; how do we differentiate if we have overlapping symptoms? So, for both depression and fatigue, we can see changes in sleep, motor slowing, a loss of energy, this diminished engagement in activities, and even diminished cognitive skills. That can be seen in either case, so how do we decide what's really going on or what the culprit is because we need to know that in order to inform our interventions and make recommendations for that. So, I find it really helpful to kind of separate these out.

[00:20:49] What are some things that, symptoms to consider that might distinguish each depression and fatigue? And so, certainly with depression we see this prolonged depressed mood, these feelings of sadness, emptiness, hopelessness. We might see weight changes, gaining or losing weight. Motor agitation, in addition to slowing would be another possibility, which we just mentioned. Feelings of worthlessness, excessive guilt, this would be associated with depression, and then recurrent thoughts of death and dying. So definitely something that would distinguish from fatigue alone. And certainly, I should say, someone could have both of these, right? Depression and fatigue.

[00:21:36] And then on the fatigue side, again if we're trying to tease all of this apart, feeling tired is actually the thing that leads to the reduced engagement in activities. Maybe someone saying I would love to go to that, I am just spent, and my gas tank is empty physically speaking, and I'm just too exhausted to do that. And then even feeling physically weak could be another fatigue related symptom. So, just a point on Dr. Hague's key findings around cognition, so what he found that the rates of impairment were significantly different, and this is really noteworthy too. So, 42 percent of patients with MS or participants with MS had cognitive impairment, and then that's compared to 21 percent of those with transverse myelitis. So, we actually do see a difference here where those with multiple sclerosis have more cognitive difficulties.

[00:22:44] And then when we took a closer look at those with cognitive impairment, we were able to see that they were more likely to have general and sleep-related fatigue problems, so that was noteworthy as well, seeing that association between cognitive difficulty and level of fatigue. So, we had, the question is, "Well, what factors might predict cognitive status in MS and TM?" And so, we created a model to look at that and put a lot of things into that model, and so in the interest of time I'll highlight for you that the thing that really stood out was we saw greater depression symptoms as increasing the likelihood of cognitive impairment. So now we have an association with fatigue-related problems, as well as depression, as it relates to cognitive difficulties. So, what does all this mean, and I'm going to hit this in really broad strokes.

[00:23:43] We know that individuals with CNS demyelinating disorders are considered to be at risk for neuropsychological difficulties. It's a very broad statement. It's really important to say not all are affected. So, but because we know this, we want to be on alert for it. As clinicians, as the individual with the condition, their caregivers, their loved ones, they all just want to be on alert and be aware that this is a possibility. The reason for that is so that we can provide interventions. There are some really fabulous things that are helpful

and that work for that. Research continues to offer us clues about targeted intervention, and as we said in the MS literature, they have shown that when they tackle one area they see improvements in other areas, and that is so exciting to me that we could get that big of a return on an intervention.

[00:24:42] So we know that there are lots of opportunities for interventions, evidence-based interventions. These must be tailored to the individual, of course. So, a note on who should be referred. So, I tie this in because we talk about tailored interventions, we go back to those earlier slides where I talked about the individual and the evaluation process, that everything is tailored to that person. Certainly, we could draw things, hearing about results from research today and maybe these things resonated with you, but to really get a great picture and snapshot about what's going on for you as an individual, a neuropsychological evaluation is a great way to go to start to investigate this and tease some of these pieces apart like we talked about.

[00:25:36] So I would say that the person with the condition and those that know you best are in the best position to decide if this would be appropriate. I would say one of the ways that I talk about how do you know; how do you know if you need this evaluation? It's a big commitment, it takes several hours, it's an investment. So, the marker for me is did the problems interfere with daily life, daily functioning? Whether that be with coping, mood, social relationships, activities, you need to do each day, participation at work, in the community, things like that. And so, if there are these concerns speaking with your primary physician or other care team professional is a great next step. And often that individual could put in the referral. And just so you have a sense of what to expect in a neuropsychological evaluation, there's a lot of information that's collected.

[00:26:38] So in addition to that, a direct assessment where we look at things like memory and attention and their clinical interviews, record review. We really want to understand the medical background. There may or may not be diagnoses made, that's not a requirement for an evaluation, but if it's applicable certainly an example of that would attention deficit disorder or a learning disability, something of that nature. What I really appreciate about what neuropsychology offers is we're all human and we're all built with strengths and weaknesses. That's just how we're built. And so, we really look for those strengths that the person has, and we leverage those to address weaker areas through the tailored treatment plan. So that's a really wonderful thing about the individual assessment, and then we create a plan for follow-up.

[00:27:32] I want to touch on a few things here at the end in terms of things that can be done, things that might be in a tailored treatment plan, certainly for mood related symptoms, maybe an individual therapy. Our last presenter spoke about cognitive behavioral therapy which has a great evidence base for addressing depression and many other things, and I have added here a picture of someone doing a virtual visit since this has become such the norm lately. A lot of our psychologists and therapists are using virtual means to deliver this care, and so it's a very convenient and safe way if you're wanting to stay socially distant from others. Exercise, we know is connected to improving mood and I always like to mention that.

[00:28:25] Getting a good night's sleep, I was just in a talk before this one that had to do with getting quality sleep and how that ties in so closely to mental health. So, in both directions, if we don't get a good night's sleep, we might have trouble with emotion regulation in our daily lives. But also, problems with sleep can be a marker for a mental health problem. If we're getting too much sleep or not enough sleep, if we can't shut down our minds at night because we're racing with thoughts, so there, sleep is such a critical component. I would almost start there as almost the number one priority. One of the top priorities, anyway. And then, there are other things here, and I know I'm going over here on time.

[00:29:13] So, just want to end with a note for caring for the caregiver for, so for any of you who play this role, remembering this analogy we bring up a lot which is be sure to take care of yourself before you care for

others, just like we would on an airplane. I know a lot of us probably haven't flown in a while, but they always announce put your mask on before you assist the person who needs your help. Same is true for caregiving and I wanted to mention that today that, so, a lot of the things we're talking about they can be helpful, or helpful for all of us and certainly relevant to the caregiver. So last slide here, mental health is health. We have to take care of our mental health each and every day just like we look after our physical health, so make time for that daily. And with that, I will stop and ask for any questions if we have time.

[00:30:13] **Roberta Pesce:** Yes. Thank you so much, Dr. Harder. This was an incredible presentation; we really appreciate it. I think we have 1 minute or so to answer a question that came in from our community. The question is, "Is there any instrument to predict which MS or rare neuroimmune disease patient is more prone to depression? Is it just the standard PHQ-2 or PHQ-9?" Do you have any insights on that?

[00:30:37] **Dr. Lana Harder:** Yeah, so that's a great question. There are so many different instruments out there and so it would come down to the clinician preference, and also based on the person's age. So, we have lots of different measures again depending on age, and exactly what we're looking at. Some of those measures are more targeted for depression or anxiety, and then some are really broad based and meant to be almost like a screener so that then we can dive deeper if we suspect a problem.

[00:31:10] **Roberta Pesce:** Right. Okay. Great. Well, thank you so much, Dr. Harder, for your time today. I know there might be some additional questions coming into the chat, but we welcome you to join on the front end to answer them if you would like. And again, we're really appreciative of your time. So, thank you. Thanks.

[00:31:25] **Dr. Lana Harder:** Thanks for having me.