

Impact of rare neuroimmune disorders on cognition, depression, and quality of life

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[00:00:00] **Dr. Michael Levy:** Good morning, everyone. Welcome to Day 3 of the 2022 RNDS. This morning we're going to get started with a presentation from Dr. Lana Harder. Lana is a full professor of psychiatry and neurology at the University of Texas Southwestern and Children's Medical Center in Dallas. And she is a pioneer in this work of psychology and cognition in children and in people with rare neuroimmune diseases and the title of her presentation this morning, the first one is impact of rare neuroimmune disorders on cognition, depression, and quality of life. Thank you for coming.

[00:00:52] **Dr. Lana Harder:** Thank you for that kind introduction and thank all of you so much for having me. I only wish I could be there in person with everyone. So, as actually being mentioned, I'll be talking about how rare neuroimmune disorders show up in daily life essentially. So, thinking mostly today about cognition, mood, and quality of life. I first want to acknowledge the patients and families impacted by these rare diseases that we're talking about this weekend. Without their stories, it would be very difficult to do the work that we all do together to try to understand how these conditions impact daily life so that we can intervene and offer treatment plans to address those challenges. So, I really wanted to start with that acknowledgment as well as acknowledging SRNA.

[00:01:47] And again thanking you all for having me we've had a long-term partnership at 10-plus years, and I always love to be a part of any of these programs where we can share the information that we're learning all the time. I also want to acknowledge my team in Dallas. They make coming to work on Fridays for clinic so much fun and it's the bright spot of my week, so I want to acknowledge each of them. I've learned so much from working alongside this group over many, many years. I like to start out just by mentioning the role of neuropsychology. I frequently get questions about what neuropsychology is and so I want to be mindful that not everyone has encountered a neuropsychologist or knows about our field.

[00:02:37] The most distinct way I've learned to describe this. To describe it is the science of human behavior as it relates to central nervous system function. So, you'll hear neuropsychologist talk a lot about cognition that you can see in this first image and how it relates to brain function very directly and specifically we also are concerned with behavioral functioning, emotional functioning and aspects of quality-of-life fatigue is a big one that we focus on and that will be the focus of this discussion for this morning. So, I wanted to just set that as the context. When I think about the work that I do, and I work with trainees and talk about it. One

of the first places we're starting in our institution is the medical condition. So, what I have here is an MRI of a teen with multiple sclerosis and we'll pretend that this is the same teen in this stock photo that I have of a teen in a classroom setting.

[00:03:37] So, the idea here is we want to understand how a condition like MS impacts daily life or shows up in daily life like in classroom learning since that's where our teams spend most of their days. The situation is much more complicated than that. So, there are a lot of things we're trying to understand at the same time too. Also, recognize that many other factors impact how any of us show up on any given day. And so, I think about this especially when a patient is coming to see me, I want to understand their background going all the way to gestation forward, understanding when they've had a medical event. What age were they? Is the disease or condition acute or chronic? And a whole host of other factors, certainly the family and school environments. How they are coping with everything that they're managing and so forth.

[00:04:39] Importantly, we want to know what supports they already have in place, and we want to look at what supports we might be able to add for them. So, this is a snapshot of what I'm doing at an individual level when I evaluate someone, I also identify as a clinical researcher and so I definitely want to acknowledge the difference in those roles. So, when I'm in there as a clinician I'm really focused on that one patient at a time, working with my team to create these tailored evaluations and recommendations for that one person. When we talk about research which we'll do today, this is more typically we're thinking about diagnostic groups. Maybe we have a set age range, for me, that's going to be the pediatric age range. We're going to have some questions hypotheses.

[00:05:29] These are things that usually arise as I interact with patients and families and hear their stories. So, I generate questions about what it means to be an individual or to have an experience with one of the conditions that we're discussing. And I'm looking very much at the group level. So, as I describe some research findings throughout the morning, that's really where I'm coming from. But the results of those groups studies can help us extract clues about how we might help those individual patients who come to see us. So, over the years, we've thought a lot about how can we compare groups in our clinic to better understand really each of those groups. As you've heard this weekend, I think MS is a much more common condition, especially in adults, not so much for children, but is more studied, it's better understood. Whereas a lot of the conditions we talk about are rarer and so a little bit harder to study.

[00:06:34] So, initially when we were thinking about good comparison groups for just first studies that we were doing as a team, we wanted to look at this well-established MS brain-based medical problem as it compared to transverse myelitis which impacted the spinal cord only. So, early on we did that comparison and we hypothesized that those with MS would have more difficulties with cognition and school problems. And what was unexpected to us is that the rate of school problems which is something we look at a lot for kids was equivalent for those with MS versus TM. We also saw that there were some cognitive problems we had not anticipated for individuals with TM. So, I would say that really was a pretty defining moment and at least in my research narrative that I wanted to take a turn and look at some things in a different way and I'll be describing that.

[00:07:36] We did go on to publish a paper on cognitive functioning and transverse myelitis. What you see in this table is the list of cognitive domains that we evaluated along with the frequency of problems or impairment that we found. So, you can see again this was really unexpected for us, because we know that TM doesn't affect the brain directly. Now we also noted there were higher rates of fatigue noted for our patients with TM. And these were pretty impressive to us. This left us with a number of questions. So, it's a great about research. You may answer one question or two questions, but then you end up with probably

many more questions than you had before. So, because in our early study we had pretty small sample sizes so we wondered if there would be differences in cognition with larger sample sizes of MS and TM.

[00:08:39] As I noted in the last slide, we really wanted to better understand fatigue that stood out to us in that TM and cognition paper. So, we wanted to know if fatigue was playing a role and also if mood impacted cognition. This was a question that was coming up over and over and conversations, we would have in clinic and our camps that we would attend in events with our community. So, we'll come back to these questions in a moment. But I started to think of MS as a control in rare disease research. So, knowing that we again have established a lot of knowledge about MS, primarily in adults, but some in pediatrics, I was very curious to continue to use this as a comparison group. So, an important point that I think we've seen over and over in our research is that cognition, mood, and fatigue are often interrelated.

[00:09:36] So, when we run our statistical analyses, we see that these things are significantly related. And that when you treat one of these issues you may get a bigger bang for your buck, because then you are also treating some of these other inner-related difficulties. So, I just want to mention that. I think it's a really important point that I'll come back to at the end of our discussion today. It's also got me thinking about who else has compared MS to a rare neuroimmune conditions. When I first started in the clinic, we did not know a lot about cognition and NMO. In fact, everything I could get my hands on at the time said there it's really relative sparing of the brain, so didn't really go there and talking about cognitive problems. But as you can see, some studies have popped up since that time, I don't expect us to digest everything in this slide. This information is really here for reference. But what I want to highlight here is that in some of the studies found no differences between NMO and MS when it came to cognitive function.

[00:10:47] Again, these are adult studies. So, but it's all we had, so as a pediatric clinician this it was very meaningful to me, because I was very aware of again how well-established it is that a large subset of individuals with MS may have cognitive problems. So, then to hear that there's no significant difference with those with NMO. I'm really you got my attention and made me think about this population differently. And I will note we screen all of our kids in the clinic cognitively regardless of their diagnosis. So, we were already on top of that. We used the screeners to then determine if we would do additional assessment. There was some research looking at pediatric MS compared to ADEM, a very small sample size nine in each group. What they did see is what we might predict based on the nature of MS being a chronic condition where you accumulate disability over time. But those with MS demonstrated more impairment on our cognitive domains.

[00:11:57] Generally, those with ADEM showed normal levels of cognitive function, but there were weaknesses identified and complex processing. So, this is what we knew as it related to MS compared to ADEM. So, going back to these questions and thinking again about MS compared to TM, my dissertation student whose now Dr. Cole Haig who's up in Boston now he did this study took this on, and really looked at several of those questions I just shared with you. So, as you can see, his title reflects that he looked at the role of fatigue, depression, and other clinical factors in determining cognitive status in pediatric MS and TM. So, in order to go down that road and think about those questions, I want to set the stage and talk about what we do know about M. S. and fatigue. It's hard to overstate how debilitating fatigue is. It's one of the most commonly reported symptoms and often the most debilitating symptoms as described by those with MS.

[00:13:08] So, as many as 75% of adult experience fatigue in the context of MS. We know that it impacts quality of life and more and more, our literature has grown to show us that this is true for pediatric patients as well, that they endorse a great deal of fatigue. And that research is still developing and expanding. In terms of MS and depression, we know that the lifetime prevalence for depression when you have MS is quite high at 50%. There's a lot of discussion and information we've learned about the role of the inflammatory process on

the brain as a biological basis for some of those symptoms. And then we know that about half of those with pediatric-onset MS meet criteria for a psychiatric diagnosis and many of those are the internalizing conditions like depression and anxiety. When it comes to cognitive problems, the estimates that we have there about half of adults with MS will have cognitive impairment. About a third of those who have pediatric-onset MS.

[00:14:19] So, in Dr. Haig's study, he really wanted to evaluate and compare fatigue and depression symptoms between groups of pediatric patients with MS and TM. And to explore the relation of fatigue and depression and cognitive status. So, I want to give you some high-level finding that I think are really important. First of all, his sample, this is a pretty robust sample when you think about. Again, the rarity of pediatric-onset MS as well as we know for TM. So, 67 with MS 53 with TM. And the measures used, we had data from a cognitive screening battery for everyone in this study as well as caregiver and patient reports on mood. And we focused in on the depressive symptoms in particular. Also looking at quality of life and focusing in on that which was related to fatigue symptoms. And that's in three areas general sleep, rest fatigue, and cognitive fatigue. So, key findings for fatigue.

[00:15:24] There were no differences when we ran the statistical analyses between MS and TM groups for all of the areas that I just mentioned. Another way that we look at this is we compare to the normative mean just to see if the groups differ significantly and in all areas of fatigue both groups were showed statistically significant worse fatigue. So, this is a really important finding, again, knowing that fatigue is one of the most common, most debilitating symptoms associated with MS to then learn that there really are not differences between MS and TM. I think really in certain ways validates the symptoms of fatigue in transverse myelitis, which is something we've wanted to better understand over the years. I think if we were to show this to folks who experienced TM, they would probably not be very surprised by these results. I think it's always good to test those hypotheses and have the data to support this.

[00:16:30] And then this table here just shows the frequency of elevated fatigue across those groups. So, what you can take away from this is general fatigue is quite comparable between MS and TM when looking at a frequency of difficulty. And then you see some differences there with sleep and rest and cognitive fatigue where that's a bit more pronounced or more common for the MS group. But still when you ran the analyses, you did not see a statistically significant difference. When it comes to symptoms of depression, and I want to emphasize that they're not diagnoses of a clinical depression. So, we were just looking at symptoms and symptom elevation. We saw no differences between groups, but we also saw no differences for the normative means. So, meaning that the symptoms and frequency of symptoms were not different than what we would expect in the general population. And you can see about a quarter of those with MS and a quarter of those with TM experience elevated symptoms of depression.

[00:17:45] So, this question comes up a lot with my colleagues with patients and families I work with. How do we know if we're looking at depression symptoms or fatigue? And I want to say it frequently is both and that's perfectly fine these things co-occur, but I do think it's important and this is a role neuropsychology frequently plays to look at how to tease these things apart. So, what is overlapping while changes in sleep, motor slowing, loss of energy, diminish engagement and activities and diminished cognitive skills like the ability to concentrate. These are things that we can see in depression or in fatigue. When we think about other things to consider, how might we separate these to better understand what's going on? The reason for wanting to separate these two, importantly is this would have different implications for intervention and treatment.

[00:18:45] So, of course for depression, we would be looking for a depressed mood, and one that's lasting, I would also say feeling sad, empty, hopeless, maybe seeing weight changes, motor agitation, feelings of worthlessness and guilt, recurrent thoughts of death and dying. For fatigue, feeling tired often leads to the

reduced engagement in activities. And we also think about the feelings of physical weakness. So, these are just some things that I think about when I'm trying to determine is this depression or is this fatigue, again or is it both? So, in Dr. Haig's study, going back to that when he looked at cognition, we were able to evaluate rates of cognitive impairment and we did see a significant difference where a cognitive impairment designation was much more common for individuals with MS which makes a lot of sense given the brain-based lesions in MS in the chronic nature of the condition.

[00:19:53] And then those with cognitive impairment were more likely to have elevated general and sleep rest fatigue problems. So, that's an association that's really important to point out. So, Dr. Haig also had the question what factors predict cognitive status and MS. So, what would predict if you were in the impaired versus non impaired group? And so, we created this model where we looked and considered all of these factors? So, a person's diagnosis levels of fatigue levels of depression, agent onset time since onset and physical functioning and the one thing that stood out that's highlighted here are symptoms of depression, so that increased the likelihood of cognitive impairment. This is a finding that we've seen across other studies and other populations as well and was very interesting to see that be the one thing that stood out in a significant way. So, what does all of this mean? And what are some of the takeaways?

[00:20:58] I think just broadly speaking, we are aware that those with CNS to myelinating disorders are considered to be at risk for neuropsychological difficulties. That's a very broad statement and I will mention that not all are affected. I work with plenty of patients that do not report these things that don't have difficulties on our testing. So, there's a lot of variability and I think that's what really underscores the importance of that individual evaluation. We can describe our research findings and what we see in a cohort, but we also, at the end of the day, I really want to know about what's going on for the person in front of us, having their research, however, helps us realize that there is that risk. And so, we want to explore that, that's why I'm in our clinic is to conduct those screeners to see where the problems are and who may benefit from additional testing and more treatment planning.

[00:21:59] So, we also think a lot about this that when we see co-occurring symptoms that if we address one of those, we may also have an added bonus of improving other areas of function. So, as I think I've said many times now, we really just want to tailor our interventions to meet individual needs and I want to talk a little bit about that. Another question I get a lot is how do you know if you or someone you know, should be referred for our services? And so, I think the people that are in the best position to evaluate that are the individuals themselves and those who are closest to those folks. Because what they can evaluate are the symptoms that we've been talking about, there could be changes over time. So, one example is, there could be a person, maybe this is resonating with someone in the audience for themselves or someone they know, maybe the change or the observation has been mood changes over time. And so, it might be a good time to explore assessment and treatment options for that. It could also be someone who's always struggled in a given area.

[00:23:17] Maybe it's paying attention or reading or insert whatever the problem is there are plenty of developmental problems or problems that had an earlier onset that maybe have gone unaddressed, unassessed, or untreated. So, it doesn't have to be that there's been a change, but maybe it's been a long-standing struggle. And then either case, what's important to really think about is how is it affecting daily life, schoolwork, interactions with friends, family, getting out to do activities. We think of that as the functional impact if it's creating a barrier to daily life. And so, what we would say is that there are concerns speaking with a primary care physician and neurologist, members of the care team could help point you in the right direction for pursuing those services. And just a note about neuropsychology. We have a really vast network across the country and even across the globe, so we are out there and can be found for these services.

[00:24:21] One thing I have the privilege of saying to my pediatric patients, which goes a really long way is I'm not a medical doctor, I don't do medical procedures and that's usually a huge relief. So, I like to paint a picture of what this looks like. Some people might be hesitant to seek services but knowing a little bit more could be helpful. So, it's a lot of question answer. It's collecting background information, reviewing of the medical record, and pulling in other information as needed and we frequently asked teachers for information, parents or other loved ones who know the patient best. We may be expert in neuropsychology, but those around the patients we serve are really the experts on those individuals. And then we are looking to identify primary problems. Sometimes there's a diagnosis and for me again that's not a medical diagnosis, but examples would be ADHD, dyslexia, autism, a whole host of things maybe depression. We are really most looking for strengths and weaknesses in that individual. We all have them. We're human beings and that's how we're made. And so, we really want to understand those strengths in order to leverage those to address weaker areas.

[00:25:42] From that, we create tailored treatment plans including a plan for follow-up. And then I just want to say a few things about wellness. I think this is important for all of us. I think that we have learned more and more over the years about what helps when we're struggling. There's a lot of great research, we've talked about depression today on therapy, on medications for depression. When you pair those you tend to get even the biggest improvement. We know lifestyle factors are really important for addressing many of the things that we talked about today getting sufficient sleep, exercise, nutrition, having a social support, a social circle all of these things go a long way for brain health and overall wellness. So, I want to mention that. I can't say emphasize this enough caring for the caregiver and so remembering to take care of yourself before you take care of others, just like we hear when we're on an airplane, we need to put on our oxygen mask before we help someone who needs that assistance. And then very importantly mental health is health and it's for everyone.

[00:26:59] And so, for anyone listening to this with or without a medical condition, make time for mental health each day. I just want to also mention in terms of support things that build us up and help us is being here at an event like this, having the SRNA community, we are stronger together. And so, I think programs just like this are what it's all about and how we can come together to improve our own situations and that for our community. And just as a final slide, some of my favorite scenes here, but I want to thank you again for having me. I was noting the time and think I just barely hit it right at 11:30 here, 9:30 for you all. Happy to take any questions at this time and I'll be talking again in another hour or so.