

Behavioral and Psychological Changes in Demyelinating Conditions

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GG deFiebre: [00:00:00] Hello everyone and welcome to the SRNA Ask the Expert podcast series. Today's podcast is entitled "Behavioral and Psychological Changes in Demyelinating Conditions. My name is GG deFiebre, and I will be moderating this podcast along with Rebecca Whitney. SRNA, or the Siegel Rare Neuroimmune Association, is a nonprofit focused on support, education, and research of rare neuroimmune disorders.

[00:00:25] You can learn more about us on our website at wearesrna.org. This podcast is being recorded and will be made available on the SRNA website and for download via iTunes. During the call, if you have any additional questions, you can send a message through the chat option available with Zoom. We would like to thank our partner, the MOG Project for contributing questions to this podcast.

Rebecca Whitney: [00:00:48] Our 2020 Ask the Expert podcast series are sponsored in part by Alexion, Genentech, and Viela Bio. Alexion is a global biopharmaceutical company focused on serving patients with severe and rare disorders through the innovation, development, and commercialization of life-transforming therapeutic products. Their goal is to deliver medical breakthroughs where none currently exist, and they are committed to ensuring that patient perspective and community engagement is always at the forefront of their work.

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GG deFiebre: [00:02:25] For today's podcast, we are pleased to be joined by Dr. Lana Harder and Dr. Cynthia Wang. Dr. Harder completed her doctoral training at the University of Texas in Austin, Texas, and completed her pre-doctoral internship at the Kennedy Krieger Institute and Johns Hopkins School of Medicine in Baltimore, Maryland. She completed her post-doctoral fellowship in Pediatric Neuropsychology at Texas Children's Hospital and Baylor College of Medicine in Houston, Texas.

[00:02:52] Since 2008, Dr. Harder has served as a Clinical Neuropsychologist at Children's Health in Dallas and as Associate Professor of Psychiatry and Associate Professor of Neurology and Neurotherapeutics at the University of Texas Southwestern Medical Center. She's board certified in Clinical Neuropsychology with subspecialty board certification and pediatric neuropsychology.

[00:03:14] She specializes in the neuropsychological evaluation of pediatric patients, from infancy to let young adults, with disorders of the central nervous system. Dr. Harter serves as the Co-Director of the

Children's Pediatric Demyelinating Diseases Clinic. Research interests include cognitive and psychosocial outcomes for pediatric multiple sclerosis, transverse myelitis, including acute flaccid myelitis, acute disseminated encephalomyelitis, clinically isolated syndrome and neuromyelitis optica.

Rebecca Whitney: [00:03:42] Dr. Cynthia Wang received her medical degree from University of Texas Southwestern Medical Center in Dallas, Texas, and completed a pediatrics and pediatric neurology residency at Mott Children's Hospital, University of Michigan Health System in Ann Arbor, Michigan. Dr. Wang completed her James T. Lubin Fellowship under the mentorship of Dr. Benjamin Greenberg at the University of Texas Southwestern and Children's Health. Her research study was a prospective, longitudinal study on acute disseminated encephalomyelitis to identify the clinical characteristics, treatment methods, and follow-up interventions that are associated with better and worse patient-centered outcomes.

[00:04:23] Welcome Dr. Wang and Dr. Harder. And thank you both for joining us today.

Dr. Cynthia Wang: [00:04:27] Hi, thank you for having us.

Dr. Lana Harder: [00:04:30] Happy to be here.

Rebecca Whitney: [00:04:31] Thank you. Dr. Harder, we'll begin our first question with you if you don't mind. The first one we've received is, can people who have TM, NMOSD, the other demyelinating disorders, get a diagnosis of PTSD or post-traumatic stress disorder? It seems a sudden paralysis or acute illness requiring hospitalization potentially with no immediate obvious cause could bring on PTSD. Is it taken into consideration by medical professionals? How common would this be in association with these diseases, and how is it treated?

Dr. Lana Harder: [00:05:09] Excellent question, and this is actually one I've considered quite a bit myself working with patients with demyelinating disorders over the last 10 plus years. A few things to think about here. I think the short answer is yes, that people who have had these neuroimmune conditions could get PTSD, absolutely. It is taken into consideration, at least as far as my clinic goes and the colleagues that I work with. I would say for anyone working with a psychologist or neuropsychologist around these conditions that that would always be on the radar of a professional like that. And probably, you could say the same for physicians, but I won't speak for them on this topic. As far as how common PTSD might be in the context of a demyelinating disorder, it is difficult to say, as it relates to the rare disorders. There is some work on multiple sclerosis and PTSD.

[00:06:07] And, that work has shown a subset actually do meet clinical criteria for a diagnosis of PTSD. And it's actually many more of those patients that report symptoms that are associated with PTSD, which there's a difference there. And this is something that we're always considering when we work with an individual patient, is do they have some symptoms of a problem or do they actually meet a clinical threshold to be diagnosed. What I have seen in my work, with children, specifically children and adolescents with rare neuroimmune conditions, are these increased symptoms of anxiety. And so in the example that was given in the question, something like a sudden paralysis is an incredible experience that could lead a person to internalize a message that, my body is unpredictable, or safety is not a given. And so we can see children show this increased anxiety following an event like this, and they seem to have a stronger need for predictability. They may show increased irritability, especially when things don't go as expected, or if there's a change in plan.

[00:07:18] As clinicians, we're always exploring this possibility of psychological problems as they relate to the child's history, not only during and after a medical event, but even beforehand. So it's important for us to also understand what symptoms or experiences that might underlie a PTSD or an anxiety.

[00:07:37] What were those things that existed even before. I would say that, I think it's important to consider PTSD in a broad sense. We think of our parents and caregivers, maybe even siblings, people who love and care for the person who's had the condition. I think thinking about the mental health of our caregivers is really extremely important.

[00:08:00] There are treatments for PTSD. There are clinicians who specialize in this area, and we are always looking for opportunities to make a recommendation to address whatever those symptoms are. I think it's really critical to acknowledge that our patients are as unique or more unique than these demyelinating disorders that uniquely impact the central nervous system.

[00:08:26] It's really hard sometimes to describe a given outcome, even if we're talking about one diagnostic group, just because there is so much variability, again, not only with the conditions, but with the patients as well.

GG deFiebre: [00:08:40] Great. Thank you so much for that. An additional question for you, Dr. Harder, is what are the potential risks of not treating the psychological impact of a rare neuroimmune disorder?

Dr. Lana Harder: [00:08:51] I think it's highly dependent on that very unique individual and the unique circumstance that they're in relative to their medical problem, but also as it relates to their history, their mental health history, and a host of other factors. So I would say this is highly dependent on the situation.

[00:09:10] But in general, we do have many well-researched tools that help people who are suffering from various psychological difficulties or disorders. I would say in general, we would want to see someone get help sooner rather than later. And this is especially important if symptoms are interfering with daily life, with relationships.

[00:09:32] But it's really of critical importance that that person is at a place of willingness to engage in treatment. So, we might say, "Oh yes, you should get help for that" or "It's good to do it sooner rather than later." But the timing is so important for that individual that may be struggling, so that they're open to that experience and able to work with a therapist. Also finding the right therapist is really important to make that meaningful change.

Rebecca Whitney: [00:09:59] Thank you so much, Dr. Harder. This next question from our community, I'd like to ask Dr. Wang. This individual said she's interested to know how aware of her illness her sister would have been during the six weeks she spent diagnosed with ADEM before she passed away. She lost all cognitive ability, but would her brain have known? She's distressed that she might have been frightened and unable to communicate that.

Dr. Cynthia Wang: [00:10:26] Yes. Thank you for that question. It's so heartbreaking to hear that. So, all my thoughts are with the family member of this person affected. And typically with ADEM, we see lots of brain inflammation, creating a state we call encephalopathy in which it can be very variable in terms of level of alertness and consciousness and thought.

[00:10:46] She mentioned that the patient didn't seem to have much response to her environment or other stimuli. If I had to surmise, again, there's no way I can know. But for most of our patients who are very encephalopathic, to the point where they may not be able to verbally respond or follow commands, it's usually a state that's really not compatible with the person having an understanding of their situation or the ability to feel pain. In that way, I would think that most likely, if she was at that state, she probably had very little awareness or understanding of the environment, and hopefully that did not contribute to any suffering.

[00:11:22] I would say in rare cases, and I think this is, again, one of the most horrifying things that can happen is, there's a syndrome called Locked In Syndrome where a person does not have any response to their outside environment, but they can perceive all the information. But again, that is very rare and usually it's more, it doesn't really happen with our neuroimmunological conditions to my knowledge, but oftentimes with different types of strokes to part of the brain called the brainstem.

[00:11:48] Again, it's hard for me to surmise, but if it helps give this person some comfort, I really do not think that their loved one was able to really appreciate or feel any suffering during her state.

GG deFiebre: [00:11:58] Thank you, Dr. Wang. And then, Dr. Harder, I'll begin with you, and then Dr. Harder, if you have anything to add. This question says, my mind is always thinking about how to manage my pain. It's exhausting and I know at some point soon I will need a caretaker, and so I fear that part too, because my medication and my pain management devices are complex. What are some coping mechanisms to deal with the psychological effects of pain and chronic illness?

Dr. Lana Harder: [00:12:22] I really appreciate this question. I think I'm going to first acknowledge the global impact. When someone is experiencing chronic pain, it really can spread into all aspects of life. Just general daily functioning, but certainly the ability to interact with other people, to think, cognitive skills in general.

[00:12:44] I think it's probably even hard for a person to really understand who hasn't been through that. And so, just acknowledging that piece of it. This is an incredibly debilitating symptom of our demyelinating disorders. And we talk about this and think about this a lot in our clinic, and even as it relates to our research. I would say that, there are lots of approaches to pain management, and I'm sure the person who posted the question is aware. It sounds like there are some mechanisms on board. Some coping mechanisms, I'll say I have many colleagues in psychology who actually specialize in pain, have dedicated their entire careers in research to pain work.

[00:13:25] And they are much better able to talk about this. And if I'm not wrong, I think we had one of them do a podcast a while back. I think what I hear the most about as being effective is a multimodal approach, bringing multiple things on board, whether that be medication or different devices as what were mentioned. Biofeedback is one that I hear a lot about within the mental health field and in psychology, which is this guided technique where actually the patient is trained to use this independently. And it's really meant to allow the patient to tune in to their body, to address those symptoms of pain in very specific ways. And this is very much tailored to that individual. So that was one thing or few things that came to mind as I heard that question. I don't know if Dr. Wang might have some other thoughts there.

Dr. Cynthia Wang: [00:14:18] Yeah, I agree with that completely. I think the first step is that, this person has started to think about these issues and knows the importance of that. I think there's a lot to be said about just that burden of having that psychological weight that you may be needing to ask for help. And, I think many people, when they talk to their caregivers, their caregivers are more than willing, and they want to do as much as they can. It's really hard, too. I think people don't want to impose on other people.

[00:14:47] So, I think it's really important that there's an open and honest conversation, potentially mediated by a psychotherapist who can help those issues come to light. Because I think it's probably most oppressive when these thoughts and emotions weigh on us and they're not being communicated to our loved ones.

[00:15:04] I think having a conversation with your medical professional, with a mental health professional, knowing evidence-based ways of coping with stressors. Maybe having contingency plans - if this were to happen, these would be my wishes and so forth. I think, again, it's so much of this needs to be

individualized for the person, their family, and loved ones. I think having that discussion under the guidance of a professional would be really meaningful.

Rebecca Whitney: [00:15:30] Thank you, Dr. Wang and Dr. Harder, always very complex questions when it comes to dealing with the pain. This next one I'd like to pose to both of you as well. And Dr. Wang, you can start off with this one. This individual in our community has said, I'm 33, female, and in the months leading up to my transverse myelitis attack, I noticed myself drinking more and experiencing blackouts. This is not something I've dealt with before and have been a social drinker since college. Could this be related to transverse myelitis?

[00:16:03] I've also noticed that I have some rage issues. I have a very short temper since the attack. And prior to this, I have always been diplomatic and reasonable. But now I seem to just snap, and I almost feel as if another person has been unleashed. Could this be an effect of the neuroimmune disorder too?

Dr. Cynthia Wang: [00:16:20] Yeah, I'd like to thank the listener for that question. Again, as a clinician, I always want to ask more questions and I know with these questions we can't. But I think there's a few things I'll point out about her question which is, even before this attack of clear inflammation, demyelination in her spinal cord, she had some behavioral and some neuropsychiatric changes and was that a part of the illness? Was that something that contributed to her developing transverse myelitis? I think those are questions that we grapple with and we don't know quite yet. I think sometimes I hear transverse myelitis and other neuroimmunological conditions can be triggered in some part by anything that's physiologically stressful to the body.

[00:17:00] So things like illnesses, but it could certainly be things like physical and emotional stressors. So, was there a reason that the individual was using that as potentially a coping strategy, and maybe that stressful life event or that time in her life was what contributed to this neuroimmunological condition.

[00:17:18] It's also possible that even without clear brain inflammation, that inflammation within the central nervous system could have had subtle effects that persisted before the attack of the transverse myelitis. I will say that generally autoimmune conditions of the nervous system, they operate on the time scale of days to weeks.

[00:17:40] So the fact that this individual had symptoms months leading up to it makes me think things that were that far back were not immediately related or a manifestation of the condition, but, again, we're learning more every day. As we get smarter about these conditions. The phenotype or the clinical presentations associated with the largest widening, we'll discuss a little bit later in this podcast. There's many questions about, as we learn about MOG, how our understanding of that disease is changing. I don't think there's ever any firm answers, but I would say if it happened many, many months before and if those behaviors related to some sort of maybe life event stressor, then I think it's more potentially a contributor, but not necessarily a part of the same disease process.

Dr. Lana Harder: [00:18:22] I don't have much to add at all, but I would say, following an event, I'll kind of zoom in on a piece of this, which relates to a rage issue, shorter temper since the attack. I would say we certainly see changes relative to emotional functioning, such as increased irritability. I know we've talked a little bit about PTSD. I think we'll get more into to this topic as we go through all of the questions. One thing that stands out I think as a strength in this case is that self-awareness and also curiosity that this individual has about this timeline of events and these different symptoms.

[00:18:57] And I think those will serve this person really well as she goes through the journey here. I wanted to acknowledge that too.

GG deFiebre: [00:19:05] Great. Thank you both so much. We did get a question that some children with MOG antibody disease experience significant behavioral changes. Why does this happen? And can it be prevented in any particular way? Dr. Wang, if you want to start.

Dr. Cynthia Wang: [00:19:22] Yeah, sure. Maybe I'll start by defining my understanding of the question. With MOG related conditions, myelin oligodendrocyte glycoprotein, depending on where this antibody strikes in the brain you can get a whole number of symptoms.

[00:19:36] Classically, we've seen children who have ADEM, now known to actually have an anti-MOG mediated ADEM or acute disseminated encephalomyelitis. In many cases, the brain is inflamed in the white matter, which is sort of what connects the different processing parts of the brain. In some cases, especially with MOG, we see parts kind of deeper in the brain, that are involved in perhaps mood, movement, emotional regulation or higher order areas of the brain called the cortex, which is where the neurons in the brain really compute all the stimulation that the body is exposed to. The behavior can be very variable just depending on where in the nervous system or in the brain the inflammation happens.

[00:20:19] And then I guess part of the question, or the way I interpret is that with the attack, the flare, the exacerbation itself, you can certainly get behavioral changes. And in fact, that is a part of the defining criteria for ADEM, that a child or adult has something called encephalopathy, which is an alteration in level of alertness, behavior, personality perhaps.

[00:20:41] That's already kind of built into the definition of acute disseminated encephalomyelitis. But I think what families probably experience more is sort of the sequelae or the aftermath of that condition in which, as the brain heals and things kind of change in terms of processing and executive functioning and decision making, things like that, then you may see other symptoms that come about just because the brain is healing. In many cases, we consider this some form of an acquired brain injury. Whether that could be related to attention, ADHD type symptoms is pretty common in kids who've had ADEM after the attack. But, yeah, I think, as relates to the question, behavioral changes are very common, both in the acute phase as well, after the condition, because of the disruptions that the inflammation may have had on the brain.

GG deFiebre: [00:21:29] Anything to add?

Dr. Lana Harder: [00:21:30] Yes. That was a great description of the brain and biology of it all. And I think it's so complex. Talking with families and patients in our clinic, I know that there's a few other culprits that I have come to recognize as certainly influencing, I think, the behavior of our kids, and maybe more so in the kind of medium to long-term.

[00:21:52] I know that, medications, I think we've mentioned earlier, steroids can alter things as well. If those are part of the treatment regimen. And while those are really important for treatment, we can also see some changes in the child, whether that be mood related, increased irritability, sometimes cognitive difficulties. Other things, just the experience of having that medical problem can change the way the child is interacting with people around them.

[00:22:17] And even family dynamics. We talk a lot about that in our clinic. I would say in response to the question on treatment that we do have many effective treatments, particularly if those behaviors persist. Often, I think, Dr. Wang and I see in our clinic that behavioral difficulties, even emotional difficulties, may improve some over time. And especially after we clear that acute phase and say steroids are out of the system and things settle back down, we can see a lot of improvement. But sometimes, as was noted, things will persist. That's why, our clinic, we follow our kids over long periods of time, we check in with them on a regular basis just to make sure those needs are met as they heal from the event, but also kind of get back to school and to life and normal interactions. I wanted to just kind of throw those pieces in as well.

GG deFiebre: [00:23:09] Great. Thank you. And just as a follow-up: have you seen the myelinating syndromes behave like anti-NMDA, where someone is completely different to their normal personality, like aggressive or acting inappropriately for their age? Dr. Wang.

Dr. Cynthia Wang: [00:23:24] That's a great question. And I think this field is changing so much and I think maybe to start all define those conditions, on how we, as clinicians, diagnose them maybe just to get everybody on this same page. I would say autoimmune encephalitis is sometimes been synonymous with anti-NMDA which is one of the best studied and most well-known types of autoimmune encephalitis. It's when the body makes an antibody that leads to inflammation because it latches to an important protein on the outside of neurons. So, it changes the way neurons interact with each other. Symptoms can be seizures. Sometimes it can be psychosis, seeing or hearing things that aren't there, having unusual or unlikely thoughts called delusions.

[00:24:07] Typically those are, again, related to changes in neuronal function, the parts of the brain where the cells are processing information. In demyelinating conditions we see inflammation more the wires connecting those parts of the brain. So, when myelin is injured, we see more of a loss of function in that the connections between things like the eye and the brain or the spinal cord and the brain are lost.

[00:24:34] And the common presentation of symptoms that are typically a loss of function, whereas an autoimmune encephalitis you see either a change in function or sometimes even a hyperactivity of brain activity, such as seizures, in psychosis. So, I think this is a great question but not one that's been asked enough and only we're only beginning to understand it now that there's some reports of anti-MOG disease with more of behavioral presentation. But we know in cases of conditions like MOG it doesn't follow all the rules. It doesn't just affect white matter; areas of gray matter can be inflamed. It stands to reason that if the same areas that can be affected by an anti-NMDA or other types of autoimmune encephalitis can lead to those symptoms if there's inflammation, regardless of the cause. Even if it's MOG and it can look at the same clinical presentation. I would say, yes, it is certainly possible just depending on where the inflammation happens. There's also this rare coexistence where people may have both MOG and in NMDA antibodies. Again is it just bad luck? Is it a coincidence? Sometimes autoimmune diseases seem to come together. So, perhaps something that triggered the MOG also triggered antibodies in the body to be made toward NMDA. I think as we learn more about these conditions and are testing more widely for them, I think this will be a clear question, but, I think that the answer for now is yes, but we don't know to what extent that that's a common or a common off of a presentation that, that we should be testing for it when we suspect an autoimmune encephalitis.

Rebecca Whitney: [00:26:10] Thank you. Another question for the both of you and Dr. Harder, maybe, we'll start this one off with you. Can a patient have a relapse with behavioral or psychological symptoms, but not have any signs of active or new lesions or MRI confirmed findings of an inflammatory attack? Some families, particularly those with ADEM or MOG have noted behavioral changes, but no new inflammation on MRI. Is this possibly due to long-term effects of an initial or previous inflammatory?

Dr. Lana Harder: [00:26:44] I think this is an excellent question. I'm actually very curious to see what doctor Wang says on this one, but I'll mention a few things, some of this is a little bit about what we touched on in an earlier question. We know that things that underlie behavior are really complex. Right? There's so many different things. And so when there is a behavioral change or emotional change, we will hear about this in our clinic. Families will contact us and a lot of times that leads to some medical testing to see is this a new event? What's going on here? Our goal is always to work with the family to both get answers but also, and really importantly, create a plan to address whatever it is that's going on. I would say it certainly is possible because I've seen it myself in our clinic. I can also say that unfortunately our literature is pretty limited when it comes to the long-term effects of things and findings are pretty mixed as far as if we're seeing any negative changes over time, or actually improvements over time. The research suggests that either of these

can happen, and looking at some of our ADEM data a little while back, we did notice that time since onset, if you were to look at kind of the point in time when the medical problems started and then kind of measure that amount of time, more time since onset was associated with more, what we call, externalizing behaviors. So that would be things like maybe aggression hyperactivity. And this was a very small sample size. Like I said, the results are really mixed, but we did notice that some changes could emerge over time, for our kids and maybe that relates to the phenomenon where we're talking about, but clearly we need more research to of get some answers around that.

Rebecca Whitney: [00:28:36] And Dr. Wang, do you have anything to add to that?

Dr. Cynthia Wang: [00:28:41] No, I think that was a great answer. And I agree with it wholeheartedly. I think it becomes tough. We only have the tools that we have and they're not perfect tools. So, with MRIs, sometimes we get complaints of people who have new symptoms of weakness or optic neuritis, changes in vision and we'll do imaging and we don't see any inflammation. But. Sometimes we'll still treat because those tools, if they're not applied at the right time, perhaps we don't catch the inflammation when it's happening. It's too early or too late. And then we've certainly seen that sometimes in cases where it's a more defined syndrome that.

[00:29:20] People get benefit from things like steroids and presumably there was inflammation, it was just not visible to either neuro imaging or the other commonly completed study would be looking at the spinal fluid to see if there are too many immune cells that would represent inflammation or encephalitis or inflammation elsewhere.

[00:29:39] Certainly it's possible. I think it's just harder to know when you don't have any objective measures for symptoms. I think there's this concept of pseudo exacerbations where, with any sort of injury to anywhere in the nervous system, if there's any physiological stressors, then your body's inability to compensate to those stressors can sometimes unmask old symptoms. So we usually counsel our patients that if they have kind of a resurgence of old symptoms the best thing to do would be just kind of wait, try to get comfortable, see if there could be any reasons that could have unmasked those symptoms, like being overheated, having a, an infection. And then if it goes away within generally, last less than a day, then it's more likely to be the type of pseudo exacerbation, or kind of unmasking of symptoms rather than representing new inflammation. With autoimmune encephalitis I think this is even more challenging because while study types of autoimmune encephalitis, like anti-NMDA, the MRI can be normal more and more than 50% of the cases. Thankfully in demyelinating conditions we are usually able to see where the white matter is inflamed, but our imaging techniques are not as good for things that affect the gray matter or the cortex. So, especially if it's more behavioral, it's possible that we may not just not be able to capture it with our current tools.

Rebecca Whitney: [00:31:00] Thank you. And this next question is for you to Dr. Wang, and I know you've talked about it a bit already, we have several questions that are pertaining to autoimmune encephalitis. Could you briefly explain the difference between auto immune encephalitis and acute disseminated encephalomyelitis?

Dr. Cynthia Wang: [00:31:21] Sure. I would say autoimmune encephalitis is more of a all-encompassing more umbrella term, which means that there is some sort of inflammation in the brain and the mechanism generally is the body making an antibody toward some protein in the brain that leads to changes in its function. And again, the characteristic ones are things like anti-NMDA, and that's often synonymous with autoimmune encephalitis, ADEM or acute disseminated encephalomyelitis is a syndrome that we have known for longer just because it's as a pre - defined demographic it's typically younger children. They have pretty acute onset within certainly days to weeks of changes in neurological function. And we can correlate that to, usually, lesions in the brain that shows that there is white or gray matter inflammation. In that way,

ADEM by definition needs to have an abnormal MRI or have abnormal neurological exam findings and it's a little bit more well defined just because for some reason it seems to happen in the pediatric age group. We know autoimmune encephalitis can really span the whole lifetime and there are certain types of autoimmune encephalitis we rarely see in pediatric patients that can happen in adults and sometimes being related to the immune system reacting to certain cancers or tumors in the body. So, I would say autoimmune encephalitis is a larger term, but many of the conditions seem to be antibodies targeted at neurons or gray matter rather than the white matter, which is what we see with ADEM and other demyelinating conditions.

GG deFiebre: [00:33:02] Great. Thank you, Dr. Wang. And then to follow up with MOG being a fairly new diagnosis and conditions that cause behavioral or psychological problems like ADEM and autoimmune encephalitis being linked to MOG, is it safe to say that those behavioral and psychological problems are also present in MOG patients?

Dr. Cynthia Wang: [00:33:20] Again, it's a very case by case basis. I've seen MOG and ADEM affect just one part of the brain, or they can affect lots of different parts of the brain. And we always try to understand the symptoms in relation to where in the nervous system that inflammation happens. So it can certainly create all types of symptoms. Generally, in autoimmune encephalitis we see the inflammation more in parts of the brain called the limbic areas that have to do with emotional regulation. In ADEM and MOG we don't necessarily see that. It tends to go for other structures in the brain, but the whole brain is interconnected. All of these parts of the brain work together in some way. And there's feedback loops that we don't know about yet. So I think any interruption or change in the circuitry of the brain, if it's involved in things such as behavior, which is so much of the brain is involved in behavior, then certainly that can lead to behavioral changes.

Rebecca Whitney: [00:34:18] Thank you. And this next one is for you, Dr. Harder. With conditions like ADEM and autoimmune encephalitis and their direct correlation with the brain, it's a bit easier to understand they're causing behavioral changes. Do the other demyelinating disorders such as NMO, AFM, optic neuritis and TM, that generally target other specific areas of the central nervous system, such as the optic nerve and gray or white matter of the spinal cord cause behavioral changes too? And does it differ in presentation, whether the inflammation was in the brain or elsewhere in the CNS?

Dr. Lana Harder: [00:34:57] Yes. Fantastic question. And one that I feel like highly relates to the research that we're doing at Children's and UT Southwestern. I would say we're working through these questions all the time and have been now for a really long time.

[00:35:13] I'm a clinician researcher and I specialize in these conditions. So, I work really hard to look at the data across groups, across these diagnostic groups, to try to understand both the commonalities and the differences. And I think when we better understand those two things where led to better and more precise treatments.

[00:35:35] Certainly we could see behavioral changes in individuals with other conditions that are not obviously brain-based, but the reason for this is really the subject of our work right now. And I I'd love to hear it. some examples of that. We early on notice some areas of cognitive difficulties in transverse myelitis, which is described as a spinal cord condition. And we were trying to better understand that through exploring possible contributing factors, using brain imaging, and also trying to understand how fatigue and mood might play a role there. We have not been able to identify any clear brain-based differences in TM, which really kind of aligns with our understanding of the condition. But my former student, Dr. Cole Hague, actually explored fatigue and depression during his dissertation. And the way that we did that and the way that he did that was comparing multiple sclerosis and TM. And the reason for that comparison is that MS is well-established area where we have a lot of research, by comparison to our rare conditions that we're

talking about today. What really struck us was that in his work he found no differences between fatigue or symptoms of depression reported in our youth with MS and TM. And the reason this was such an important finding is MS is, as we know, a chronic brain-based disorder with this very well-established research on the incredibly debilitating symptoms of fatigue, as well as high rates of depression. So to learn that there were no differences between MS and TM was incredibly eye-opening to us as clinical researchers. Another finding there was that fatigue and depression were each associated with cognitive impairment. So that starts to give us some clues about what might drive some of these differences across conditions. I think that we'll have a chance to talk a little bit more in depth about some of these things as we move through our podcast.

GG deFiebre: [00:37:37] Okay. Thank you so much. And then are demyelinating conditions likely to affect brain functioning directly? And also what are the long-term effects of a demyelinating attack that causes behavioral or psychological changes, specifically children who are still growing and do not have a baseline established yet? Dr. Wang?

Dr. Cynthia Wang: [00:37:57] Yeah and I'm very much want to hear Dr. Harder addressing this question too, because I think it's very much in her wheelhouse, but I really like one thing she said in the past, discussing these concerns with our families, our children. And it's the fact that you can grow into your deficits. So if a child had ADEM at a very young age and the demands of life and school are very low, it's possible that as academic challenges, social challenges, become more heightened as the child gets older, that there are things that kind of come to light. I think the fascinating, but also difficult thing about working with children is that there's so many changes in the lifespan of a young child, and there's so many natural changes in behaviors that we see as a child gets older and kind of forms their own identity. Changes related to hormones, such as puberty. So I think trying to understand these conditions sort of on a moving target, if you will, is one of the things that I certainly want to get Dr. Harder to weigh in on too. And I know she studied this in some of our patients.

Dr. Lana Harder: [00:39:05] Yes. And I agree completely with what Dr. Wang said. These are some excellent points, especially as we think about our patients in a long-term way. I feel like I might be repetitive and saying we're still learning about this. So this is a focus of our research. And a lot of the research that exists is what's called cross sectional. So it's a snapshot in time describing a cohort of patients. There is much less longitudinal or kind of that long-term data where we track the same patients over time to see how they do. I think one of the most important things we can do is compare a patient to him or herself over time. And that's what we're able to do when we follow patients, as they age and develop and grow just like we do at Childrens. So we track them, try to understand how they're developing and what they need at that given time. As Dr. Wang said, in response to those increased expectations that they have. Just based on the fact that they're aging and growing older and becoming what we hope to be more independent. And just as a reference point, when we think of the status of our research, pediatric MS, which I know I've mentioned here a few times, that area of focus in the research really only emerged in about the early 2000s. That's an area that is more developed and we have some work to do in that respect. I would say there are some mixed findings in the research, some show improvement over time, especially if there's only one event versus chronic conditions where the central nervous system continues to be impacted. But even in those cases, and even in the MS literature where, we believe that disease process can have a more severe impact on the developing nervous system, even that literature shows some improvements and some declines. So it's very mixed. Some stay the same. So we don't have this really clear picture about the long-term outcomes, which I know is not a very satisfying response to give.

[00:41:05] And just worth saying again, that we still have a lot to learn. I would say things that we see the most, that I think can undermine a person's success in daily life, would be challenges with fatigue that seems to be prominent pretty much across the conditions we take care of in our clinic. And then risk for

internalizing symptoms. And it may not be a full-blown diagnosis, but symptoms of anxiety or depression, and fatigue and emotional symptoms can really work against a person who's working to go to school every day and to learn and to function as independently as possible. I really want to highlight that those are two areas we see pretty commonly and would want to track very carefully because we know that when there is research to show that when we address those problems, we can see positive outcomes in other aspects of life.

Rebecca Whitney: [00:41:54] Thank you so much. We've received a couple of questions live that are pertaining to how someone would find and seek support. And, one individual has noted that they've had NMO for 31 years and feels as though they don't have emotions and is wondering if their neurological condition affects the ability to feel emotion. They've tried to get into a neuropsychiatrist, but they only take people who are declining. Another has indicated that they're listening in from the UK and that the mental health services there are very poor, and someone with a condition like TM might have an extra need for emotional support, in addition to the treatment of their physical symptoms, seems not to have a place in their healthcare system. What methods are available for testing to help determine a psychological baseline, to know where someone's starting and how they're changing? What doctors should be involved to conduct testing to determine a baseline and assess for changes? In addition to neuropsychologists, would neurologists, other subspecialties play a role in this area? Where should people start looking for support from the health care system? Dr. Harder, if you'll start with that one.

Dr. Lana Harder: [00:43:13] Sure, happy to kick this one off. Welcome Dr. Wang's input as well. I think in Dallas, Dr. Wang and I are big fans of this multidisciplinary approach to care and to assessment, to treatment. We really appreciate the chance to work within a team. And if the team is not assembled under the same roof or institution, doing what's possible to link those professionals or get them to communicate, I think is best case scenario. Also, not always possible. But in terms of the question around developing this baseline, in our medical setting it can be really difficult to get a true baseline since we usually encounter our patients once they've had some kind of medical event and we're working to understand the outcomes of that event or of a specific diagnosis. But, for kids or adults who maybe have had some type of evaluation prior to onset of medical problems, maybe that was testing in a school or working with a psychologist or neuropsychologist, and had some type of assessment, having those documents can be really incredibly valuable for having that baseline. Documentation of something that predated the onset of a medical problem. But I would say, most of the time we don't have a true baseline and that is perfectly fine but getting an assessment sooner rather than later to establish the current baseline lets us track a person, an individual, over time. So we compare that individual to him or herself to see how they've responded to treatment, how they developed in their cognitive problems, if there's been - and it's very unusual to see - but if there's been a regression or for kids, if there's been a failure to keep up with their peers, our tests are really made to compare people to others their age.

[00:45:02] Getting an evaluation, you can still sort of have this baseline from which you compare things subsequently, which I think is a really great value to have when you're especially undergoing different treatments. Going back to an earlier question, you're going to work on addressing pain or fatigue or elements of cognitive problems.

[00:45:21] We know that when we address one of those things or a few of those things, we can see this great return in other areas like cognitive function. I think having that evaluation is great. Neuropsychologists do that, psychologists do that, when it comes to that standardized assessment, but there are many other assessments that our medical colleagues perform as well.

Rebecca Whitney: [00:45:41] Thank you so much. Dr. Wang, did you have anything that you would like to add to that last one?

Dr. Cynthia Wang: [00:45:47] Yeah, I agree. I think part of the question was also the types of providers. I think neurologists are good at doing exams, looking for things like weakness, changes in muscle tone, called spasticity. Oftentimes there are physical symptoms that can be brought out on exam, and something can be done to help if there are physical symptoms of muscle stiffness, tightness, neuropathic pain, which oftentimes are very much interlinked to mood and emotional health. So yeah, I think truly a multidisciplinary approach.

[00:46:19] And, there are the people who are there to diagnose the conditions. And then there's also the people at the front lines, working with a person such as psychotherapists, counselors. And I just wanted to bring up, I think it's very intuitive in our patients who've had conditions like transverse myelitis, especially if they have trouble with mobility and control of their movements, to seek physical therapy, it's sort of just apparent to everybody. But when the inflammation happens in the brain, which is such a incredibly complex organ and really responds to everything that we're exposed to in life, I think that there's a role for a psychotherapist who is the person who helps people recover and heal from that injury. I think sometimes there's this black or white, like is this a neurologic condition? Is this psychiatric? I saw that as a theme with some of the questions.

[00:47:11] And, as far as I know, there's only one brain and we're two types of specialists looking at the same organ, how we study and how we conceptualize is different. But, I think as we're getting better in understanding the basis, the physiological and the biological basis of psychiatric conditions, it's only hopefully going to get better in how we're able to care and treat the underlying causes of these conditions.

GG deFiebre: [00:47:35] Great. Thank you so much. And then, if someone might be seeing a primary care physician for example, how can they better educate primary care doctors or even neurologists about including demyelinating antibody screenings when patients present with symptoms like psychosis or altered behavior or seizures? Dr. Harder.

Dr. Lana Harder: [00:47:56] I think about this a lot, just educating people, other providers, whether those be physicians or people like me in psychology and neuropsychology. And I think there are several things. I think that those of us in academic medical centers can write papers, present at conferences. I think that SRNA is an amazing organization with efforts to reach out to different providers to provide that education. Those are some things that first come to mind. But I know how critical it is for primary care, even emergency medicine providers to have this on their radar. I'm not sure if Dr. Wang has other ideas on this.

Dr. Cynthia Wang: [00:48:38] I think people on the front lines, they really have it tough because they see all types of conditions and when it's a rare condition, just even being aware of it may be difficult. I think since we have such an educated listenership, sometimes the family feels motivated to do the research themselves and it can be sometimes a helpful thing to provide papers or provide articles from SRNA to their physician. And, unfortunately, medicine sometimes can be a discipline where people can have some ego, and being given something can seem a little bit disarming to them.

[00:49:13] I think it's just having a dialogue in approach and not just having a conversation, "I found this resource, would you mind reviewing it" and being very respectful of how you approach that. I think at any point, the fact that SRNA exists, and it can be so helpful to community providers. We're always welcoming questions from physicians, from families and give some general advice to families and help. We're very willing to talk to people's providers and see a patient, get a referral if it makes sense.

[00:49:42] I think it's a little bit hard, and I know our specialists are not available in all communities. I think if there's one good thing from the COVID epidemic, it's that telemedicine has really allowed us to reach out to people that we normally would not be able to see in clinic.

[00:49:57] So, I've seen people across the United States. Now is a time where it's somehow become easier because of some external challenges to provide our specific medical opinion. I don't think, as a whole, general practitioners, such as pediatrician, internists, or general neurologists should necessarily be the ones to order these tests because as we learn more and more about them, it becomes much more nuanced. I do think it makes sense if you think you may have one of these diagnoses to seek out a specialist who just sees those conditions.

Rebecca Whitney: [00:50:30] All right. Thank you so much. And thank you, Dr. Wang and Dr. Harder for joining us today. I know we have several more questions that we had previously and have additional questions that have come in live as well, that we're not able to get to within the hour. So, we'll hope to schedule another podcast shortly, to perhaps address those, and we'll make sure that we hold on to those questions so that we can get some answers for our community. But I just wanted to say thank you very much again. And, did you have any final thoughts that you wanted to share today before we end this particular podcast?

Dr. Lana Harder: [00:51:08] I would just say, first of all, thank you for having us. This is a topic I think you can tell Dr. Wang and I feel strongly about, and we appreciate the interest and all of the wonderful questions. If it wasn't made clear, I think it's always important to acknowledge that these conditions are incredibly unique, as are those who have experienced them. And we see a whole range of outcomes, individuals who almost seem to not be affected in some of these behavioral and psychological ways that we've been talking about today. But all the way down a spectrum of those who are severely impacted. And, it just makes me want to emphasize the importance of an individualized approach, as well as a team approach, multiple specialists need to be involved to care for individuals with demyelinating conditions. I just wanted to acknowledge that, but thank you again for having us.

Dr. Cynthia Wang: [00:52:00] Yeah, and I, again, also like to thank you. This was a really interesting discussion. It's always difficult when we can't back up what we think with some evidence, and hopefully that will change. And I'm looking through some of the questions and comments. It seems like there're increasing patient organizations, including a lot of parents of children who have MOG disease who have firsthand seen the behavioral and the neuropsychiatric changes that can come with the condition. And I think it's really important that they engage with their medical community, as well as the SRNA to help inform us as researchers and clinicians on what are the important questions to ask. Because that's the only way we can move forward in our understanding and treatment of these conditions.

Rebecca Whitney: [00:52:42] Thank you. Thank you again, both so much. And we'll keep working to answer questions from both sides for these disorders. With that, we'll close, and keep your eyes and ears open for future podcasts.

Dr. Cynthia Wang: [00:52:57] Thank you.

Dr. Lana Harder: [00:52:58] Thank you.

GG deFiebre: [00:52:59] Thank you.