

**CURE Epilepsy Webinar
Identification and Treatment of Autoimmune Epilepsy
(Transcript)**

- Dr. Laura Lubbers: 00:00 Welcome everyone to today's webinar. I'm Laura Lubbers and I'm the chief scientific officer of CURE Epilepsy. And I want to thank you for joining us today. Today's webinar is entitled Identification and Treatment of Autoimmune Epilepsy and is intended for everyone, including persons with epilepsy and their caregivers. Our body's immune system is what protects us from harmful viruses, bacteria, and more. Autoimmune encephalitis refers to a condition that occurs when the body's immune system mistakenly attacks healthy brain cells, leading to inflammation or encephalitis of the brain.
- Dr. Laura Lubbers: 00:37 As a part of the immune system's response, the body produces antibodies that often at different receptors in the brain, which leads to different forms of autoimmune encephalitis. Symptoms of autoimmune encephalitis may include seizures, memory loss, cognitive problems and impaired speech, autoimmune associated epilepsy may also result. And it's important to diagnose because this type of epilepsy does not generally respond to typical antiseizure medications. Instead, immunotherapy is often used to treat people with this condition because it reduces inflammation in the brain.
- Dr. Laura Lubbers: 01:15 This webinar is the first of CURE Epilepsy's, 2022 Leaders in Research Webinar Series, where we highlight some of the critical research that's being done on epilepsy. Today's webinar, like all of our webinars, is being recorded for later viewing on the CURE Epilepsy website. And you can also download transcripts of all of our webinars for reading.
- Dr. Laura Lubbers: 01:37 For over 20 years, CURE Epilepsy has raised millions of dollars to fund epilepsy research, that supports our mission, which is to find a cure for epilepsy by promoting and funding patient-focused research. CURE Epilepsy provides grants that support novel research projects, and that advance the search for cures and more effective treatments. To date, we've raised over \$85 million to fund over 270 research projects from investigators around the globe.
- Dr. Laura Lubbers: 02:06 Today's webinar will help viewers understand the difference between paraneoplastic encephalomyelitis, which is an inflammatory disorder of the brain and autoimmune encephalitis. As well as the difference between acute symptomatic seizures related to autoimmune encephalitis and chronic autoimmune associated epilepsy. Viewers will learn about the characteristics and biological mechanisms of

autoimmune encephalitis and when to suspect autoimmune related seizures and epilepsy.

- Dr. Laura Lubbers: 02:37 This webinar is presented by Dr. Stephen VanHaerents, an assistant professor in neurology and medical education at Northwestern University Feinberg School of Medicine. His practice focuses on the medical and surgical treatments of epilepsy with particular emphasis on the treatment of medically intractable seizures. His clinical research interest include neurostimulation, identification and treatment of autoimmune associated epilepsy and new-onset refractory status epilepticus also known as NORSE. Additionally, Dr. VanHaerents is deeply involved in medical education and currently serves as the director of medical student education and neurology.
- Dr. Laura Lubbers: 03:18 He also serves as the co-chair for the Neurology, Neurosurgery, Health equity, Diversity and Inclusion Committee at Northwestern.
- Dr. Laura Lubbers: 03:27 Before Dr. VanHaerents begins, I'd like to encourage everyone to ask questions. You may submit your questions anytime during the presentation, by typing them into the Q&A tab located on your Zoom panel, and then click send. We'll do our best to get through as many questions as we can.
- Dr. Laura Lubbers: 03:43 We do want this webinar to be as interactive and informative as possible. However, to respect everyone's privacy, we ask that you make your questions general and not specific to a loved one's epilepsy. So, with that, I'd like to turn it over to Dr. VanHaerents.
- Dr. Stephen VanHaerents: 03:59 Hi everyone. And thank you, Dr. Lubbers, for that warm introduction and thank everyone for having me. I'm very excited to be here and we are talking about a topic that's very important to me and my clinical practice and my patients. So, without further ado, we'll get started. Okay. Sorry, one second. Getting used to advancing the slides here. So, the learning objectives actually, Dr. Lubbers went through pretty much already, so I won't spend too much time on the learning objectives. And instead, we'll kind of get started.
- Dr. Stephen VanHaerents: 04:38 And I do want to have a few disclosures because unlike other treatments in epilepsy, autoimmune encephalitis actually has no FDA-approved treatments. And so, I'll be discussing treatments that are actually, they're all off-label usage. And I think we'll likely be doing a follow-up to discuss full treatment options, but we'll start with a case where I will discuss some treatments for that particular patient.

- Dr. Stephen VanHaerents: 05:10 So I think it's great to put all of this in the context of a particular patient of mine. And he's doing very well now and knows that I'm presenting him individually. And so this is a case of someone who had a more subtle kind of presentation. So he [inaudible 00:05:31]. He is a 69-year-old gentleman, and this is back in 2014 where he was noted to be very confused. A neighbor initially saw him and he looked like he had just kind of woken up and seemed sort of out of it. They have a cottage up in Wisconsin. And so, his wife came back from their cottage and found him very confused. She was clearly very concerned about this and he was unable to remember the deaths of family members. His parents had both passed away. He couldn't remember that.
- Dr. Stephen VanHaerents: 06:04 So she took him to a local emergency room. It was not Northwestern, my hospital. So, I have not met him yet, but this was at another hospital where at first their initial concern was had he had a stroke? And so, they got a CT and MRI of his head. And when that came back on revealing, they did an EEG. And for those of you unfamiliar, that's the electrodes on the head looking for evidence that you might have seizures.
- Dr. Stephen VanHaerents: 06:38 So essentially, he was discharged from the emergency room. There was no stroke found. There was no evidence of seizures found at that time, but he wasn't any better. And in fact, he just continued to get worse. He had difficulty with his memory. He was unable to work effectively anymore. He had actually had to retire from his position and take early retirement. He continued not to remember that his parents had passed away.
- Dr. Stephen VanHaerents: 07:05 He stopped sleeping as well. He would stay up till about 5:00 AM when he would always be in bed by midnight. He was losing weight. And his advanced, what we call ADL activities of daily living, started to decline. He wasn't able to do tasks around the house, pay bills, more advanced-type tasks. He was just overall declining. And in addition to that, his behavior and mood were also changing. He was more irritable. He was aggressive. He was always a very kind man. And he actually left bruises on his wife's arm. And then he was also more affectionate than usual. He reported some low and depressed mood and he had also become very OCD. He couldn't leave his house without double checking things anymore, which was not his previous behavior. And overall, he was just, as his wife put it, a different person.
- Dr. Stephen VanHaerents: 08:00 In addition to these behavioral changes and cognitive decline, he was also having these episodes, which they called panic attacks. They believed it actually started maybe a few years before the onset of the confusion, but now were happening up

to 20 to 30 times per day. And when digging deeper into these panic attacks, he described them, he would breathe heavily, and words were hard to get out. And then his face would kind of get pulled into this kind of frown. And to them, it looked like he was about to cry and it would last just a few seconds. And they thought it was triggered by when he realized his memory was poor or he was forgetting something.

Dr. Stephen VanHaerents: 08:41 They also noticed he was getting goosebumps a lot, very frequently and he would start to breathe. And then it would look like he was going to cry again. When asked about it, he said it would feel like almost an adrenaline rush. Other than that, he really didn't have a significant medical history, social history or family history.

Dr. Stephen VanHaerents: 09:01 And on his exam, it was fairly unremarkable. His temperature was a little low. When you examined him on his basically mental status exam he was a little pressured meaning that he was very talkative. I remember he was very fixated on talking about apples, for instance. And he would really just talk about whatever he wanted to talk about and he had to be constantly redirected. He really couldn't form memories. I would have him try to memorize three words. And as you can see here on this exam, he could remember one of the three words in five minutes. So, his memory was quite poor. Meeting him for the first time, he had several of these episodes of rapid breathing and his mouth being pulled into a frown and then kind of forgot what he was talking about and asked what to do before the spell. The rest of the exam was really unremarkable.

Dr. Stephen VanHaerents: 10:02 I know most of you or all of you are not physicians, but what is the differential, meaning, what is wrong with him? Does he have early dementia? Is this all psychiatric or behavioral? And then what do you do if you're a family member or if you're a provider, what do you tell the patient? What do you tell the family if you're a caregiver? And what is his prognosis? What are you going to do? So maybe we'll circle back to him, but let's review this sort of workup. And how as someone who deals or treats these types of patients, how we approach this.

Dr. Stephen VanHaerents: 10:48 So before that, I think it's good just to talk about what are these antibody-associated autoimmune disorders because there's a lot of terminology out there if you're on Google. And there are a lot of overlapping terms, there's autoimmune epilepsy, autoimmune encephalopathies, autoimmune encephalitis, autoimmune dementia. And really, they all kind of mean the same thing. There are antibodies that are directed towards functional proteins that are in the nervous system and wherever

they are affecting the most is the symptoms you're going to see. So the brain, we try to separate neurology and psychiatry, but they're really inseparable because they're one organ, they're the brain. So you can get lots of dementia, psychosis, you can get seizures, you can also get movement disorders. If it's affecting blood vessels, you can get strokes. And so, there's a lot of these overlapping kind of syndromes and you may have more than one kind of bucket.

Dr. Stephen VanHaerents: 11:52 So this has been a field that has been rapidly expanding and our knowledge of it has been rapidly growing. So, when you look at autoimmune neurology from the '80s till now, it's really an exponential growth in the amount of literature that is available.

Dr. Stephen VanHaerents: 12:12 Now let's talk about some other kind of definitions, things that get thrown around a lot, there's an entity called paraneoplastic versus non-paraneoplastic and then limbic versus non-limbic. So, let's go through what people mean when they say these types of terms.

Dr. Stephen VanHaerents: 12:29 So when people talk about paraneoplastic conditions, this really just means neurologic disorders associated with some underlying cancer, but caused by mechanisms that are not, for instance, if someone has breast cancer and the breast cancer is spread to the brain and is now causing weakness or even seizures, you don't typically refer to that as paraneoplastic, it's usually directly neoplastic and you would actually call it tumor-related epilepsy as far as the seizures. So, it's not usually referred to metastatic or metabolic nutritional from the cancer, infections related to maybe some chemo or immunosuppression from the cancer. So, it's usually reserved that it's related to autoimmune disease. And what our thought is on that is that the immune system is really trying to attack the cancer, but in doing so ends up attacking normal tissue as well.

Dr. Stephen VanHaerents: 13:30 So then there's the limbic system. So, what does it do? And I actually teach this lecture to our Northwestern medical students, and I give them this little mnemonic called HOME, H-O-M-E. And it really kind of defines what the limbic system does. And limbic system is really a very old part of the brain. We call it the archicortex for those more pathologically inclined. You have the hypothalamus, which is really in charge of homeostatic functions, like autonomic with blood pressure, heart rate, temperature control, neuroendocrine kind of control, hormones, pituitary.

Dr. Stephen VanHaerents: 14:13 In fact, I had one patient, she was 27 and looked like she was post-menopause. She had stopped having periods. And that was

one of her initial symptoms from her autoimmune encephalitis. And she would later go on to have multiple seizures, which is how she came to me. But really, one of her first symptoms was really the lack of periods. And like I said, a lot of these things come in patterns and affecting multiple parts of the brain.

- Dr. Stephen VanHaerents: 14:42 Olfaction is your sense of smell and people don't ever really complain of that, but it is involved in the limbic system. The two things that people tend to notice the most is their poor memory through an area called the hippocampus and emotions and drives from the amygdala, both of which are very much affected as part of the limbic system. But autoimmune encephalitis doesn't have to be limbic encephalitis. Limbic encephalitis is essentially these structures. And so, if antibodies are attacking these structures, it's a limbic encephalitis. If they're not, then it's not limbic encephalitis, but it can be other forms of encephalitis. Because encephalitis really just means brain is inflamed. Encephalopathy means the brain is not functioning well. It's important to just kind of recognize these terms, it's overlapping, but also different.
- Dr. Stephen VanHaerents: 15:37 And so for those of you who like [inaudible 00:15:41], I'm going to go through kind of two arms of our immune system that will kind of help understand because this does affect how the treatment is and how severe the actual syndrome is. So, let's just take a look at who gets autoimmune encephalitis, who gets autoimmune epilepsy. And so, there's really three main camps. There's those that are paraneoplastic like we talked about, maybe they have an ovarian teratoma or a thymoma in thymus and your immune system is trying to attack that.
- Dr. Stephen VanHaerents: 16:21 There's also links to certain viruses like HSV encephalitis. There is now a very clear link with HSV encephalitis leading to another autoimmune condition called anti NMDA receptor encephalitis. And that's been very well documented at this point. So, there's definitely viral prodromes as well.
- Dr. Stephen VanHaerents: 16:43 And then there's idiopathic meaning we have no idea how it happens. And some of these patients having had a lot of these idiopathic, there might be some sort of genetic predisposition like lupus or other autoimmune diseases run in their family, or they have other autoimmune conditions as well. So, it's unknown exactly what caused it, but sometimes there does seem to be some risk factors.
- Dr. Stephen VanHaerents: 17:09 And so now let's break our immune system into two pieces. You who have B cells and T cells. T as in Tom. So, B cells are bone marrow-derived that they become these cells called plasma

cells and plasma cells then make antibodies. And so antibodies are supposed to recognize foreign things for instance viruses or bacteria.

- Dr. Stephen VanHaerents: 17:35 But if they're making antibodies that are autoreactive, meaning recognizing your own neurons, they can bind to things, for instance, an NMDA receptor or something on the surface of a cell that then is activated with the inflammation and can get destroyed leading to sometimes damage of those cells. And those are B cells or cells surface antigen targets, as opposed to this other side, T-cell, which is predominantly T-cell mediated diseases. Now would these little green antibodies hit things, they can destroy it.
- Dr. Stephen VanHaerents: 18:12 But what if the protein the antibodies targeting isn't outside the cell at all, then these antibodies actually can't reach this protein. And this happens with some of these intracellular targets. And so, when you see antibodies derive against intracellular targets, the antibodies aren't so much toxic themselves, but more of a marker that the cell is being injured. And it's probably being injured by the cytotoxic T cells.
- Dr. Stephen VanHaerents: 18:42 So B cells, these antibodies, if you take these red antibodies and you take them from one mouse and [inaudible 00:18:51] let's say an NMDA receptor encephalitis, and you put them in a healthy mouse that other mouse will then also become sick because these antibodies are just so toxic to the brain. Well, these antibodies, like I said, are markers. They can't actually reach their target. So, they really aren't that damaging, but these diseases are still autoreactive with these T cells and still is causing a lot of damage.
- Dr. Stephen VanHaerents: 19:21 Moving on. My little arrow here, there it goes. All right. So, I'm trying to be a lumper and not a splitter, but there's a lot of different antibodies and we're discovering new antibodies all the time. Oops. Now I advanced too far. Going back one slide. I'm sorry. I think there's a lag so now I'm reversing because I hit the advanced button a few too many times. Oops. And it's still advancing forward. Okay. So here we are. Oh, now we're back to there, but I'm going to just stop hitting it and I can talk from memory. I know what the slides say. So, the cell surface ones are going to be examples like NMDA receptor encephalitis maybe you've heard of voltage-gated calcium or LGI1 encephalitis. All of those are the cell surface. There it goes. So, voltage-gated calcium channel, all of these are these cell surface where the antibodies are directly toxic as opposed to the intracellular ones.

- Dr. Stephen VanHaerents: 20:52 And the intracellular ones are anti-hu, there's [inaudible 00:20:57] there's CRMP-5, amphiphysin. There is also GAD65. And with the exception of GAD65, almost all of these are highly associated with cancer. So the intracellular ones are very frequently paraneoplastic as we were talking about, related to an underlying malignancy or cancer.
- Dr. Stephen VanHaerents: 21:24 Okay. So now let's talk about seizures, since this is CURE and the E is epilepsy. So, seizures are well recognized, a prominent manifestation of autoimmune encephalitic syndromes. So, patients with systemic autoimmune disorders are at increased risk for seizures. So, the term autoimmune epilepsy was initially suggested as a concept in 2002, but there's been an emerging body of evidence suggesting the autoimmune mechanisms in a subset of patients with epilepsy. So the International League Against Epilepsy, the ILAE now has a category of an immune etiology for epilepsy. However, many of the patients with cell surface antibodies that we were just talking about, can actually reach complete seizure freedom after treatment. And so, this is kind of counter to the whole concept of epilepsy, which is this enduring kind of predisposition to unprovoked seizures. So in response to that, in 2020, this was further divided into two broad categories.
- Dr. Stephen VanHaerents: 22:38 You have acute symptomatic seizures, secondary to autoimmune encephalitis and autoimmune associated epilepsy. And the acute symptomatic seizure secondary to autoimmune encephalitis are typically those cells, surface antibodies like LGI1 anti NMDA receptor. And it's thought that these antibodies are antibody-mediated ectogenesis because those antibodies are toxic in themselves and lead to seizures. And if that immunotherapy is started quickly, they could be cured, essentially of epilepsy, long term. That doesn't always happen particularly, and I'll show on a slide later, if there's a delay into immunotherapy, you can lead to damage to the brain itself and can still have seizures, but you have the possibility of kind of more of a cure.
- Dr. Stephen VanHaerents: 23:36 Autoimmune associated epilepsy is more complex, this is often in GAD65 or those intracellular antigens. And they have persistent epilepsy after acute autoimmune encephalitis. And it's thought that their epilepsy is due to ongoing, basically brain inflammation, but also structural damage as well. So, they're kind of getting it from both sides and they're usually very medical, they don't have to be, but often, especially if you make it to my clinic, their anti-seizure medications are often ineffective. They might have had epilepsy surgery with an incomplete response, immunotherapy usually with a poor

response as well. So, they're very difficult to treat and you really kind of throw everything at them. But at the end of the day, pharmacoresistant, meaning that at least two medications have failed, is not uncommon and they often will have cognitive deficits as well.

Dr. Stephen VanHaerents: 24:44

And this is just kind of showing that these acute symptomatic seizures secondary to autoimmune encephalitis. So, the green line is when the first seizure stop, the red line is when their last seizure stopped. And the blue is when they were able to come off seizure meds all together and each little notch is a year. So essentially those with cell surface in the study, 25 of them did amazing. The ones with the intercellular didn't, essentially, but they continued to have seizures. You weren't able to get them to stop.

Dr. Stephen VanHaerents: 25:22

So let's just talk about autoimmune-related seizures, are they different than other forms of epilepsy? And how are they different? So one key thing that kind of will might set you off. Is there early medical intractability meaning, from the start, the seizures were very hard to control. They usually lack other typical epilepsy risk factors, such as seizures with high temperatures as a child or family history of epilepsy.

Dr. Stephen VanHaerents: 25:51

The seizures tend to be very high frequency, but short duration, not always, but quite often. And they won't have a lot of that postictal confusion. Sometimes the first onset of status epilepticus or continuous seizure activity. That's common in this GABAa and b autoimmune encephalitis, multiple seizure types as well. So typically, if there's a structural lesion or other types of epilepsy, it'll be one type of focus and one sinology, but they'll have multiple.

Dr. Stephen VanHaerents: 26:26

EPC is called *Epilepsia partialis continua*. And that is a chronic seizure, it could be really small just like a finger, going back and forth, but it's persistent and hard to treat. It's not always autoimmune, it's usually from a structural lesion like swell or brain tumor, but particularly if no clear lesion is found, you should think mitochondrial or autoimmune as well.

Dr. Stephen VanHaerents: 26:52

And then there's specific antibody associations like LGI1 which is faciobrachial dystonic seizures, where they get this kind of either face gets clumped down or arm, and they're really fast. And I'm going to show you a video of that. GAD65 is associated. I definitely have patients with musicogenic epilepsy. They often have a very distinctive music trigger that can give them this reflexive seizure and this kind of perisylvian semiology in this area of the brain that gives you a lot different, it's actually the

next slide, if it advances, but can give you kind of auditory or language dysfunction. Autonomic with elevated heart rates, language difficulty, so very unique, which aren't always common epilepsy types. Looking at all these different types of perisylvian. And this is from Gillinder in Australia, looking at these and almost all of these patients in the study had anti-GABA encephalitis.

- Dr. Stephen VanHaerents: 27:56 So let's just look at a patient with faciobrachial dystonic seizures, just because you can kind of see one. And as I play this, you'll see they're very brief. So, he sits up in the chair here and then he has this brief kind of tonic contraction of his arm there and then it's done and it can be of the leg too. They can fall. It might just be the face or it can be all of them. They usually don't have much of an EEG correlate, but if they do this, this black is really just the EMG, that's the muscle contraction itself. But sometimes you see this kind of attenuation or loss of kind of frequencies.
- Dr. Stephen VanHaerents: 28:42 So why is this such a difficult diagnosis to make? Is it rare? Well, it's rare as much as we look for it. So, this is from Mayo Clinic where they actually looked at the prevalence and found that it was comparable to infectious encephalitis, except this is increasing over time. I don't think it's because it's a new disease. I think it's because we're looking for it more. So, it's probably not as rare as we originally thought.
- Dr. Stephen VanHaerents: 29:10 Heterogeneity of clinical presentations, well, different antibodies affect different parts of the brain. So, they're going to have different presentations, but the more we learn about it, some of these antibodies have very specific and very stereotypical type of presentations often.
- Dr. Stephen VanHaerents: 29:27 Send-out panels. This is true. There's a lot of different send-out panels from a lot of different companies and different labs can have patents and things. And so it can make it very hard to send a comprehensive panel, not to mention you can have insensitive false negatives. You can also have positive reactions to brain sections because not all the antibodies that we even know of are commercially available. There's a delay in getting the results. It can take 10 to 14 days and there's antibody negative disease. We're kidding ourselves if we think we know all the antibodies at this point.
- Dr. Stephen VanHaerents: 30:04 NMDA was discovered in 2007, for many of the people on this call, that wasn't that long ago and that's one of our best describes. So we're constantly discovering new antibodies. And then there's low-titer false positive, just being these kind of low,

basically not a ton of antibodies, but it's hard to know what to do with that. For instance, you can have GAD65 in the blood, which isn't as helpful as if you see high-titers in the spinal fluid and they can mimic other diagnoses.

Dr. Stephen VanHaerents: 30:44

So these are kind of clues to clue you into an autoimmune etiology, kind of things we talked about our patient in the beginning of this like change in baseline neurologic function, kind of fairly rapid onset for an Alzheimer's or dementia. It's pretty fast. Can have a fluctuating course. They might have other systemic markers of autoimmunity, like an ANA or TPO antibodies, which are in the thyroid. They might have a malignancy or they have an inflammatory CSF findings, abnormal EEG or MRI. So, this is a study that we did at Northwestern, looking at these TPO and ANA antibodies.

Dr. Stephen VanHaerents: 31:27

And we basically found that while they're not specific in any way, they were really elevated in our patients. And for those with having present, it was 45%, 35% and 32% of the patients tested. And prevalence of these antibodies has been previously put in disease free population. So, it is interesting that having three of three or even just having one of three positive was actually fairly sensitive, even as much sensitive as the MRI at times. So, while not specific, it can help point you in the right direction.

Dr. Stephen VanHaerents: 32:13

So while this can be overwhelming, I'll walk you through kind of an algorithmic approach of how I approach these patients and how I teach my medical students and our residents to approach these patients as well. And then we'll circle back to the clinic patients that I presented. So, in the serum or the blood, I usually check those paraclinical markers like an ANA or TPO, and then I'll get a spinal tap. I'll look and see if there's anything inflammatory. And I send this panel out and then I'll get brain imaging and look for any swelling in the brain, I look at the EEG, if there's any slowing spikes. And then I often get a PET of the brain too. And then I screen for any underlying malignancies.

Dr. Stephen VanHaerents: 33:03

And so going from there, I just wanted to give you some caveats too. That there are lots of different panels. So I try to encompass as broad of a panel as I can, but looking at specific symptoms, for instance, MOG, which you might see in the white matter of the brain, little lesions and can also present with seizures. GFAP can look like a meningitis. And so, depending on the case, I'll add on additional antibodies or additional panels as well. I never order a single antibody though. I always order a panel because the symptoms can be overlapping. And for instance, they might have LGI1 with those spacial brachial

seizures that we looked at, but maybe they have some other antibodies too, that are more linked with cancer. Because you can have more than one antibody at a time. And I usually try to use labs that have research as part of them too.

- Dr. Stephen VanHaerents: 34:04 Especially if the antibody panel comes back negative, they can look at mouse brain and see if there's any autoreactivity at all. And essentially, it's also important to look at the blood and the spinal fluid because there's certain antibodies, there are only available in one or the other. And for instance, NMDA can be negative in the blood, but it's positive in spinal fluid and LGA1 can be positive in the blood, but can be negative in the spinal fluid. So you really kind of need to give both and you have to be aware, one thing is that there's not always a ton of inflammation in the spinal fluid. And this is from Quebec where they looked at the spinal fluid and in a quarter of them, there was nothing inflammatory in spinal fluid.
- Dr. Stephen VanHaerents: 34:59 And so to help us, there are these predictive tools to help find if these are all autoimmune or not and what is suggested. And so this is the APE and our right score. And they looked at patients with epilepsy of unknown etiology and found which ones actually had autoimmune encephalitis and they developed this scoring system. And they're really not that different. And I won't go through the whole thing, but it's really kind of what we're talking about, but I'll just score it with you that patient we were talking about.
- Dr. Stephen VanHaerents: 35:33 So new onset rapidly, progressive mental status changes that developed over one to six weeks or new onset seizure activity within one year of evaluation. So, that would be the patient I discussed. So that's a point. Neuropsychiatric changes, agitation, aggressiveness, emotional lability. That would be a point. Autonomic dysfunction, sustained tachycardia, which is high heart rate, blood pressure falls.
- Dr. Stephen VanHaerents: 35:58 He didn't necessarily have any of that. So, we did not get a point. He didn't have a viral prodrome. So those panic attacks, I don't know if you noticed in the presentation, but they actually were all faciobrachial seizures. Initially, he was having 20 to 30 of them a day and his face would get pulled down. They really weren't panic attacks at all. They were actually all seizures. So, he actually gets total of five points.
- Dr. Stephen VanHaerents: 36:22 Facial dyskinesias you see with NMDA receptor encephalitis. Seizures refractory to at least two anti-seizure meds. He didn't know he was having seizures yet. So can't really give him a point yet on that. And then he hadn't had a spinal tap or MRI yet, but

he was already at five points. And even just based on that would not even be able to score the whole thing. Anything greater than four is a high likelihood that they will have an antibody positive. And so this isn't as popular of a paper, but I do like to use it. It's By the same author as the scoring, that essentially over four, even if you don't have the antibody panel back yet it's worthwhile to just try an immunotherapy trial at that point.

- Dr. Stephen VanHaerents: 37:18 So let's just talk about seizure medications real fast, because as we talked about seizure meds, autoimmune epilepsy is characteristically very resistant to anti-seizure medication. Interestingly, carbamazepine was found to be more effective than levetiracetam in reducing seizures and LGI1 encephalitis. I don't take too much out of that, except that sodium channel blockers tend to be good for focal epilepsy. So, I do try to use them in autoimmune patients, but recognizing that they need immunotherapy as well.
- Dr. Stephen VanHaerents: 37:55 I'm just going to show this because I think this is a very meaningful diagram and this is looking at those faciobrachial dystonic seizures. And the red is administration of seizure meds alone. And this is seizure meds with immunotherapy, and this is the ongoing seizures. And you can see there's a huge drop-off with immunotherapy as opposed to seizure meds alone.
- Dr. Stephen VanHaerents: 38:20 And this is, I think the most startling in that if you look at delay in start of immunotherapy in days and the likelihood of getting rid of the seizures, essentially it drops. The longer you wait, the less likely you have that they will go away. So, let's conclude with the case that we were talking about.
- Dr. Stephen VanHaerents: 38:43 So just to recap, so this gentleman is in his sixties, he had a sudden onset change and a cognition. He ended up having to retire early. He had developed OCD, he wasn't sleeping at night. He was having very frequent panic attacks and really those panic attacks, his face would look like it was pulled to a frown and sometimes he would have goosebumps and he would feel an adrenaline rush. And so, when I met him, unfortunately, this was months into this course. And so, when I met him, I immediately was very concerned.
- Dr. Stephen VanHaerents: 39:24 He also had low sodium on his labs, which you can see with the specific antibody. And then I put him on EEG. And for those of you who seen EEG, in this one, he's having a seizure from his right temporal lobe and then he had a seizure from his left and then another one from his right. And so basically, he was having lots of seizures. And if anyone remembers the antibody, I don't think you can answer. I usually give this live, these types of

lectures, but it is LGI1. He did come back voltage-gated potassium with LGI1 encephalitis. And he was negative for cancer in his malignancy screen.

- Dr. Stephen VanHaerents: 40:13 So we did initiate treatment for him. I started something called plasmapheresis to get the antibody washed out. We got steroids and intravenous immunoglobulins, and he's actually doing amazing now. He actually had to be on antipsychotics for a while and he's now off. And he was on valproic acid, but he wasn't tolerating it. And he switched over to levetiracetam. And if you remember with his type of antibody, you can be cured of seizures, long term. But with him, he continued to have sharp waves on his EEG. So, he has remained on 500 milligrams twice a day, but he's had no further seizures and he's actually off immunotherapy now as well. And so that was pretty much the lecture.
- Dr. Stephen VanHaerents: 41:06 I do want to thank our former fellow and Sebastian, who is at the Mayo Clinic and Claude, who's at NYU, and that's pretty much it. I can open for questions.
- Dr. Laura Lubbers: 41:18 Great. Thank you so much, Dr. VanHaerents, that was a lot of information and we've got a lot of great questions and we know that you've got more. So, we're hoping that we can bring you on back to share more information, but let's start in with questions. There's some great ones here and I too, I'm anxious to hear the answers. So, the first question, could infections like Lyme, Babesia or Bartonella be possible causes?
- Dr. Stephen VanHaerents: 41:49 So any infection is possible. So, I actually did my training in Massachusetts, so I've definitely seen lots of Lyme, but Lyme, one, it's very inflammatory. Typically, if it's invading the spinal fluid, but post-infectious, it's always possible. But at this point, there is no links to any bacterial-type infections. The only clear link at this point that I'm aware of is [inaudible 00:42:21] virus and NMDA.
- Dr. Laura Lubbers: 42:23 Interesting. Okay. Thank you. I'm sure there's more to learn though, there.
- Dr. Stephen VanHaerents: 42:27 There's definitely more to learn.
- Dr. Laura Lubbers: 42:30 Can you tell us about seizures that originate or localize in the brain stem?
- Dr. Stephen VanHaerents: 42:41 So that is more of an animal model thing, but there definitely is autoimmune encephalitis that also very much attacks the brain

stem. I am almost like, how much time do you? The brain stem is a very content area of the brain. And so, you can have a lot of different symptoms. In one form that attacks the brain stem, they do get myoclonus, but they have a lot of sleep dysregulation as well. A lot of times when things are involving deeper areas of the brain though, seizures are not a prominent manifestation, it tends to affect more like movement disorders and coordination just because that's what that area of the brain does more than actually seizures themselves. So, I typically actually don't see a lot of those patients, but people tell me about them, but they tend to see my movement disorder colleagues more.

- Dr. Laura Lubbers: 43:40 Interesting, again, so much to learn about the interconnectivity of the brain and how they manifest in terms of seizures or other changes. So, could autoimmune epilepsy manifest itself as a focal seizure? I think you've kind of addressed this, but [crosstalk 00:43:59].
- Dr. Stephen VanHaerents: 43:59 Yeah. It's almost always focal seizures, when they generalize it's secondarily generalized. So as opposed to a genetic generalized epilepsy, which affects both sides of the brain at the same time, even when they have a full generalized convulsion, it's usually secondarily generalized.
- Dr. Laura Lubbers: 44:17 Okay. Interesting. Here's another question. Do you see intracranial hypertension in your patients?
- Dr. Stephen VanHaerents: 44:23 I'm curious why that question was asked.
- Dr. Laura Lubbers: 44:30 We've got a great audience.
- Dr. Stephen VanHaerents: 44:33 That's an interesting question. There's sort of idiopathic intracranial hypertension, which I definitely have in my clinic as well, and maybe there's some link that they're alluding to, but I don't know of any link to autoimmune encephalitis, especially if they had preexisting hypertension. That being said when your brain's inflamed, you can get rises of intracranial pressure, for sure.
- Dr. Laura Lubbers: 45:06 Okay. Here's a more treatment-related question. How close are we to getting IVIG infusions, FDA approved?
- Dr. Stephen VanHaerents: 45:26 I'm curious if this question is geared more towards to get insurance to pay for it, which is always that all that I do in my clinic. And so, there was a trial with IVIG at Mayo Clinic for LGI1 encephalitis versus placebo. So IVIG is probably more on its way

than many others, but I'm not involved in the FDA process. So, I actually don't know.

- Dr. Laura Lubbers: 45:55 That's fair. Maybe we can come back with an answer to that. Here's another treatment-related question. Is there a next step if immunotherapy and antiepileptic drug treatment does not work? Or do we not have anything at the moment?
- Dr. Stephen VanHaerents: 46:15 I never give up, really. So, there's lots of forms of immunosuppression. So, when we were talking about B cell and T cell mediated therapy, so for instance, it was in the newspaper and she signed a media release, but we had a patient with an NMDA receptor encephalitis who was in a coma for about five months. And we could not get her to wake up. And we used plasmapheresis, IVIG, steroids, rituximab. She even got a chemo drug called cyclophosphamide and nothing touched her, essentially. And so, we used a newer chemo drug that she had been used in Europe called [inaudible 00:47:00], which is chemo for multiple myeloma, which is a B cell malignancy. And she woke up from that.
- Dr. Stephen VanHaerents: 47:07 So there's lots of different therapies. I didn't talk about the ketogenic diet either, which seems to have anti-inflammatory properties to it as well.
- Dr. Stephen VanHaerents: 47:16 And there's also anti-interleukins to anti IL-6, IL-1, which gets used in those kind of NORSE and fires cases if people know what that is, but that is a whole separate lecture. So, what do I do if initial therapy doesn't work, is I try more. But that being said, sometimes you do palliative surgeries. If one area is structurally very damaged, you could consider surgery or neurostimulation too with various nerve stimulators or even invasive neural stimulators have been used in patients that are autoimmune as well. So, you don't give up.
- Dr. Laura Lubbers: 47:56 Right. Never give up. Never, ever give up. And we also don't give up on the research. We keep looking for solutions. So, I'm glad you brought up the ketogenic diet as well. I think that's helpful for people [inaudible 00:48:10].
- Dr. Stephen VanHaerents: 48:10 I have a GAD65 patient who is doing fantastic with ketosis. Not for everyone, but it's definitely worth a try in autoimmune patients.
- Dr. Laura Lubbers: 48:27 Okay, great. So here's a bit of a longer question. For patients who have long-term epilepsy following an autoimmune encephalitis, who continue to have seizures that don't respond

to medications, what evidence have you seen for the effectiveness? Well, actually this is the question, ketogenic diet in reducing inflammation systemically. So, you've already answered the question.

- Dr. Stephen VanHaerents: 48:49 Yeah. In evidence, I don't think there is a large amount of evidence in that cohort. It's more case by case. And I do have patients that it's been very helpful for, but I don't want to say that it's been helpful for all of them. I definitely have some that it really didn't seem to budge. Some people are just very refractory, a lot of things, they don't budge in their seizure frequency.
- Dr. Laura Lubbers: 49:15 Okay. I'm just curious about this as well. Could you elaborate on musicogenic seizures in this context, any recommendations how to proceed when certain types of music are seizure triggers? And what test panels are most appropriate?
- Dr. Stephen VanHaerents: 49:31 Very good question. So musicogenic seizures, there was a case series on it and some people it's pop music and things like that, but I treat them mostly just like any other seizure, we're trying to get their seizures under control. So, I don't necessarily treat them any differently. It depends if somebody has a photic sensitive epilepsy as well, and there's certain glasses you can avoid, but you can't avoid the sunshine or something like going through trees and things. There's certain things you just can't avoid. And so really the answer is immunotherapy and seizure meds to try to get your seizures under control long term. It's just more of an interesting phenomenon of reflex seizures that GAD65 seems to get
- Dr. Laura Lubbers: 50:31 Interesting. Okay. So, somebody comments, great lecture and has the question, what's the best timing to taper off of an AED in cases of autoimmune epilepsy? How do you go about that?
- Dr. Stephen VanHaerents: 50:47 So we don't have a good answer to that. We don't even know who needs long term therapy. So, I'll just tell you what I do, which is what people more senior with more gray hair did. And so I just do it that way. So basically, it kind depends. I never wean seizure meds and immunotherapy at the same time. Because if you have a breakthrough seizure, you're not going to know which one you actually need. So that's rule number one. And so I essentially, like for instance, that guy just told you, LGI1 can be monophasic and we don't really know who's going to relapse and who's not. So, in that patient I slowly wean off. For instance, I was giving him pulse steroids, so I was giving him a thousand milligrams of Solu-MEDROL. Sorry, I should use generic names, Methylprednisolone, every week.

Dr. Stephen VanHaerents: 51:42 And I just slowly increase the time of the pulses. So, if it was every week and then every other week, and then as you're weaning off the immunotherapy, if they relapse, then [inaudible 00:51:54], you give them something long term. So, it depends on the severity too. If they were very severe like an NMDA, I'll often just continue immunotherapy and everything for about two years, that's what most people do. And then try to wean after that. Now, if they get off immunotherapy, things are going well, then I'll probably wean seizure meds too, and see if they can get off. And then I usually do a follow-up EEG and see if there's anything epileptic as well.

Dr. Stephen VanHaerents: 52:27 Then I tell them there're always [inaudible 00:52:30] too. So, if they're driving and things, I don't like them driving at that time too. And I discuss seizure precautions and things because they are at risk still for seizures. So, I just try to be extra careful in how I counsel patients as well. So, there's a long answer.

Dr. Laura Lubbers: 52:52 But I think that's helpful to understand timeframes and how to approach this. I think it's a really, especially if we think that somebody could come off of an AED and therapy. You do that. There's such a risk in that. So, thank you. Here's a different question. Can multiple food allergies contribute to these autoimmune issues? What about the body being in a constant state of inflammation?

Dr. Stephen VanHaerents: 53:17 That's a tough question. So, there is more, we're learning about the gut microbiome and how it relates to the brain. I don't think we have any specific links. There's a lot of research that needs to be done in that, some of which is being done at Northwestern, actually with gut microbiome and effect on the central nervous system. But there's also key things for instance, people with gluten and celiac disease, which has a very well documented neural celiac and neuro antibodies. So, I think long story short is we don't know, I don't know how to answer it better than that. There's some links, but to the core autoimmune encephalitic antibodies, I am not aware of any true clear associations besides for celiac disease.

Dr. Laura Lubbers: 54:16 Okay. Again, more to learn.

Dr. Stephen VanHaerents: 54:21 More to learn.

Dr. Laura Lubbers: 54:23 And I think we've got time for just a couple more questions. So can you tell us about mass cell activation, triggering seizures?

Dr. Stephen VanHaerents: 54:33 Mass cell activation. I'm not an immunologists and so I would defer that question to allergy and immunology who really treats those patients. That's kind of beyond my scope of practice. I don't want to say anything incorrect. So, I'll pass on that one. Sorry.

Dr. Laura Lubbers: 54:58 Okay. That's fine. So just to clear up a little confusion, what was the drug you referenced to treat your patient? Was it a form of ivermectin?

Dr. Stephen VanHaerents: 55:18 Okay. [inaudible 00:55:19], is that what they're referring to? [inaudible 00:55:20] is a cortisone inhibitor. Are you talking about the nurse or the patient in the case? The patient in the case got interviewed as immunoglobulins steroids.

Dr. Laura Lubbers: 55:27 Yes. And I think that can get confused for ivermectin, we've heard a lot about that lately. So, what is IVIG?

Dr. Stephen VanHaerents: 55:36 So IVIG is, intravenous immune globulin, essentially when you donate blood, your blood gets divided into, it's essentially donor antibodies, long story short. It's concentrated donor antibodies from multiple donors and then it gets concentrated and put into an IV bag. So, when you donate blood there's red blood cells, platelets, clotting factors, they separate it all out depending on what the patient needs. So intravenous immune globulin is really donor immunoglobulins.

Dr. Laura Lubbers: 56:10 Okay, great. Complicated. Thank you for [inaudible 00:56:15].

Dr. Stephen VanHaerents: 56:15 Yeah. So basically plasmapheresis... I'm sorry. I should have explained this more. So, what I did for him is I plasmapheresed him, taking out his abnormal antibodies. So, you wash their blood in five cycles. So, they're hooked to a machine and you essentially are washing out their antibodies. And then I gave him basically donor antibodies.

Dr. Laura Lubbers: 56:34 Okay. Wow.

Dr. Stephen VanHaerents: 56:37 Sorry. Yeah. I probably should explain what that meant. Sorry. I'm glad you asked.

Dr. Laura Lubbers: 56:42 I'm glad you were able to address it, though. So, we are coming up at the top of our hour. So, I will say that this concludes our webinar on autoimmune epilepsy. I want to thank you, Dr. VanHaerents, for a great presentation and to our audience for some stellar questions. Really, really engaging and really interesting questions. If you have additional questions about

the topic or wish to learn more about any of CURE Epilepsy's research programs or webinars, please visit our website or email us at [research @CUREepilepsy.org](mailto:research@CUREepilepsy.org). And we know that Dr. VanHaerents has more information on potential treatments for autoimmune epilepsy. And so we're going to try to get him back here next month. So please do stay tuned for more information about that. And also please stay tuned for announcements of our other webinars that will be coming on in the next few months. So, thank you again, Dr. VanHaerents, thank you to our fabulous audience as always, be well.