

**CURE Epilepsy Webinar**  
***Autoimmune Epilepsy Treatment Considerations***  
**(Transcript)**

- 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 a follow-up from last month's webinar and it's entitled autoimmune epilepsy treatment considerations. It's intended for everyone, including persons with epilepsy and their caregivers. In the previous webinar, we learned about the difference between paraneoplastic and autoimmune encephalopathies, as well as the clinical characteristics and pathophysiology of autoimmune encephalitis. We also learned when to suspect autoimmune-related seizures and epilepsy, and the approach to the diagnosis of autoimmune encephalopathies. And this webinar is the second 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.
- Laura Lubbers: 01:03 For over 20 years, CURE Epilepsy has raised millions of dollars to fund epilepsy research that supports our mission, which is defined 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 and funded over 270 research projects from investigators around the world.
- Laura Lubbers: 01:31 Today's webinar will provide information to help you understand more about autoimmune epilepsy and the different treatment options in considerations, including immunotherapy for autoimmune-related seizures and epilepsy. We are joined again 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 treatment of epilepsy with particular emphasis on the treatment of medically intractable seizures. His clinical research interests include neuro-stimulation, identification, and treatment of autoimmune associated epilepsy and new-onset refractory status epilepticus, which is also known as NORSE. Additionally, Dr. Vanhaerents is deeply invested in medical education and currently serves as the director of medical student education and neurology.
- Laura Lubbers: 02:24 He also serves as the co-chair for the neurology and neurosurgery health equity, diversity, and inclusion committee

at Northwestern. 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 click send. We'll do our very best to get through as many questions as we can. 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. With that, I'll turn it over to Dr. VanHaerents.

Dr. Stephen VanHaerents: 03:01

Thank you Dr. Lubbers and everyone at CURE for inviting me and having me back for a second talk on this really important topic. I will review a little bit from the last talk is Dr. Lubbers kind of went through that we discussed differences between paraneoplastic and autoimmune. I do have some disclosures and we'll be discussing because this one's more focused on autoimmune treatments. Just keep in mind there really are no FDA-approved treatments for autoimmune epilepsy or autoimmune encephalitis. And it is really lacking. Everything is kind of based more off expert opinion and case reports. This will all be kind of off-label treatments just so you're aware of that as well. Last time we talked about an older gentleman, I thought this time we would start with a younger woman and for another case. And this one's also a little challenging.

Dr. Stephen VanHaerents: 04:06

This was a 29-year-old patient of mine who was otherwise healthy, who actually came to me after loss of consciousness in a motor vehicle accident. And this was back in February, 2015. So we'll have some time to see how things progressed. At the time a truck driver had actually seen her. She was on the way to an outlet mall actually. And a truck driver saw her kind of slumped over and thought that he saw her actually shaking and convulsing. She recalls the paramedics arriving and being very agitated and combative after that. There was no other episodes that she was aware of loss of consciousness. I mean, she endorsed one glass of wine the night before, but really not as a lot of significant medical history, but when digging a little bit more, she had endorsed that she'd started having these episodes of anxiety that started coming out of nowhere, starting in October.

Dr. Stephen VanHaerents: 05:02

And now this is the late winter, early spring of the next year. She started seeing a psychiatrist and they put her on antidepressants, but really didn't have much of an improvement. She was having these, what she described as flashbacks of her childhood. And they would last a few seconds but could be 20 times per day. She was also getting these episodes that she described as goosebumps on her left arm and left leg. And they

would abruptly appear and disappear. And in the clinic, she was also describing she was having several of them. Did you hear that these kind of auditory hallucination, she described them as these high pitched beeps. Additionally, she was brought in by her sister who is, I should say, a nurse. And so was also concerned about her behaviors and how she had been acting. Over the past few months, she besides changes in behavior and what we had talked about, she'd also lost 20 pounds.

Dr. Stephen VanHaerents: 06:04

She seemed more confused. She didn't seem to be sleeping at night. She was not requiring sleep. She started taking Ambien to try to sleep, but really didn't sleep. And interestingly, she stopped having periods as well. Her past medical history, she does have a sister with Graves' disease and another sister with hypothyroidism. And then a maternal cousin with bipolar. There is some mental illness, but also some autoimmune diseases in the family. Other than that, there really wasn't any significant history. She was currently living abroad with her husband, and she worked selling brewer's yeast actually. She completed college and she was an intelligent woman. This was very erratic and didn't have any personal psychiatric history or epilepsy history. On exam, she was very tangential, meaning that it was very difficult to carry a conversation with her.

Dr. Stephen VanHaerents: 07:06

She just was speaking very quickly and would kind of veer off in her conversations. And it was really hard to redirect her. I should mention too, she lived on a military base and at the time President Obama was the president and when asked current events who was the president she said Osama Bin Laden then corrected herself later to say Obama, but she lives on a military base. And so, she sees pictures of Obama everywhere. She also had very disinhibited. She had become a nudist when she was pretty fairly conservative before and had a very significant change in her behaviors. Let's kind of review a little bit of what we talked about last time. How do we diagnose and then we'll focus this talk more on treatment. Remember last time when we talk about autoimmune disease and autoimmune disease can be directed apart, any part of the body, but we're focusing more on the brain when we're thinking about autoimmune encephalitides or autoimmune epilepsy and paraneoplastic is when it's related to cancer and nonparaneoplastic when it's not.

Dr. Stephen VanHaerents: 08:23

And limbic vs non-limbic, if we remember sorry, paraneoplastic being not caused by nutrition but more related to the immune system and the limbic system just reminding us an older part of the brain where certain viruses and antibodies can attack. And this is really what it does. It's involved in the hypothalamus, which is homeostatic functions, which can include

neuroendocrine control. If you remember that patient, she had stopped having menses and periods. They can have high heart rates, autonomic changes. They can have olfaction memory difficulties and emotions and drives behavioral changes would be amygdala. All of these would be considered a limbic kind of encephalitis because this is what the limbic system does.

Dr. Stephen VanHaerents: 09:17

And then we talked about last time, too, that you just trying to simplify the immune system that who gets these types of diseases. And we talked about that some time is related to paraneoplastic, sometimes there's viral associations and sometimes we just don't know how they ended up developing these immune systems. And then there's B cells which go to plasma cells which make antibodies and this is more cell surface where the antibodies can attack outside the cell. And then there's intercellular targets, which this is more T cell-driven with these and the treatments for these two are different typically while you would want to target against these types of cells that are making antibodies for these ones where the antibodies are directly toxic, as opposed to this line where these antibodies are thought to be more markers of destruction, because the antibodies can't actually reach their targets.

Dr. Stephen VanHaerents: 10:23

And just some examples of these types of cell surface antibodies would be like voltage-gated potassium with LGI1 Caspr2 and MDA receptor encephalitis, which you might recognize from Brain On Fire, that Netflix movie and excellent book. Then there's AMPAR, GABA-B and mGluR5, but these are all directly toxic type antibodies as opposed to the intercellular ones which besides GAD are often associated with cancer and are harder to treat. They can have a very limited response to immunotherapy. How do we start working up essentially autoimmune epilepsy and autoimmune encephalitis? We talked about last time how we first start with just blood work, looking for markers of autoimmunity like an ANA and a TPO. And we looked at a study from here at Northwestern showing how prevalent those were. Then we also send an autoantibody panel to see if any of those commercially available antibodies come back positive.

Dr. Stephen VanHaerents: 11:35

And then we look at the spinal fluid to see if there's any inflammation in the spinal fluid, which could be either white blood cells, which are inflammatory cells or elevated IgG index, which are the immunoglobulin themselves. And are they being synthesized there with these things called the oligoclonal bands where you can see if there's unique antibodies present in the spinal fluid? And then you look at the brain structure itself. Is there any swelling in these areas that you're concerned about, any other signs of inflammation? And then you look at the EEG

itself, is there slowing in these regions, is there epileptiform activity. And then there's also certain EEG patterns like extreme delta brush, which you can see in NMDA receptor encephalitis. And then a brain PET is another kind of scan which you can look at in which you have the patient essentially fast.

Dr. Stephen VanHaerents: 12:34

And then you have them get this sugar in their system, which is labeled and that sugar essentially, you're looking at how does the brain utilize that sugar. So sometimes it's very bright because it's very metabolic, either having seizures or just very swollen, just very active and so it'll be bright, or it can be very dark meaning that area of the brain is abnormal right now and not using the glucose very well. And this can pick up sometimes dysfunction that the brain MRI did not show. And so it's another area to kind of look at if you're unsure. We don't always get the brain PET, but it's a good add-on study as well.

Dr. Stephen VanHaerents: 13:17

And then you do the malignancy screen depending on if a certain antibodies came back, what might help direct but usually you start with either CT of like the chest, the abdomen, the pelvis. If it's NMDA, you really want to look at the ovaries if it's female or testicles in a male patient. You might even need to get a colonoscopy. It depends on sometimes with the antibodies and what types of cancers they've been associated with.

Dr. Stephen VanHaerents: 13:52

So then we kind of went through that and then we talked about predictive tools. Using kind of this cookbook or scoring from the Mayo Clinic and Dr. Dubey's group. And we talked about this APE2 score and the RITE2 score. And so, the APE2 is what is the likelihood that you'll get one of these antibodies coming back, because it can take a while to get the results. And then the RITE score is almost the same score, but it's when it's back, what is the likelihood that they will respond to treatment? Thinking about this scoring with our young woman, so essentially she had this new-onset rapidly progressive mental status changes that developed over one to six weeks and did have new-onset seizure activity within the year. So, she would definitely get this point. Neuropsychiatric changes, agitation, aggressiveness, and emotional ability.

Dr. Stephen VanHaerents: 14:51

She definitely gets a point. Now at this point in our evaluation, the other ones were less clear. She hadn't had a brain MRI, she hasn't had a spinal tap yet. We haven't treated for any seizures thus far. It's hard to know if she's refractory and then facial dyskinesia are these kind of normal facial movements. Often, you'll see these in NMDA receptor encephalitis, and then there's facial brachial dystonic seizures, which if you remember that patient I presented in the last webinar had those. Now this

young woman had sometimes what I think of as the sensory equivalent, where she was getting this kind of rush of cold and chills with these goosebumps. And if you remember, we talked about how autoimmune seizures tend to have this kind of predilection to this perisylvian region. Despite her only having concretely two points, I'm suspicious at this point, and we need to get more work up in this patient essentially.

Dr. Stephen VanHaerents: 15:58

We also talked about how do you use this when you're waiting for autoantibody panels? If the score goes above four and you're still waiting for it to come back, then you do something called an immunotherapy trial. If you've excluded other diagnoses as well, you have to exclude alternative etiologies, and then you have to finish the workup. But that's what we're going to focus on today, this part, instead of just the diagnostic piece. Let's start her evaluation. Even just checking her temperature 96.2, I'm not saying that's super abnormal and a lot of people, especially if the thermometer wasn't kept in the mouth very long can have a lower temp, but in this patient, I'm a little concerned because we already know a 27-year-old who's not having periods now out.

Dr. Stephen VanHaerents: 16:51

I'm already concerned about some of those autonomic, that hypothalamic dysfunction we were talking about. And then her sodium was also low, which you can also see in these autoimmune patients, particularly in the anti-voltage-gated potassium channels. The rest of everything was fairly unrevealing. She had a 30-minute EEG, which came back normal. Her brain came back normal, and she had a CT looking for any tumors and that also came back normal.

Dr. Stephen VanHaerents: 17:26

Interestingly, we started this workup as an outpatient because I had a high degree of suspicion, but her behaviors became increasingly erratic to the point that she was actually, for those of you who visited Chicago, know the area of the Loop, which is a very dense area. And she decided to start streaking without closing through the Loop. To which point we brought her into the hospital that we needed to do this work up a little bit more expedited. At that point, she's placed on continuous EEG and remind you that the first 30 minutes that she had just had done a few days prior was normal. But in between that when left unprolonged, even though many of you cannot read an EEG, the odd numbers are the left side of your brain, and the even numbers are the right. And essentially, she starts having seizures coming from the left temporal here and she starts having frequent seizures.

Dr. Stephen VanHaerents: 18:29 She's having lots of seizures that really kind of went unnoticed. She would stop essentially when staring at her, the first one she was just having difficulty reading, probably just zoned out. The second one she did kind of look around and had what we call oral automatisms where she stared off and she was smacking her lips fumbling with things. And then afterward she had difficulty talking, which she recognized something was wrong at that point. The third one, she was just very confused. The fourth one, she was trying to play cards and became confused. And the fifth one was actually while she was sleeping. At this point, we know that she definitely is having seizures at the very least. So, she is loaded with a seizure medication and phenytoin was the one chosen. Now, if you remember, we talked about seizure medications and there's not a ton of evidence of what works better, but in one study particularly with LGI1 encephalitis, we did find that carbamazepine seem to be more effective than levetiracetam.

Dr. Stephen VanHaerents: 19:39 And so this family of sodium channel blockers, I do tend to favor and phenytoin is one that can be given IV. So, you can get into the system very quickly. However, knowing her desire to have children later and I think Dr. Gerard has given you a webinar from Northwestern before and talked about reproduction, that this is probably not the best choice long term. And so, the plan was to transfer her over to lamotrigine, which is much better studied for women with epilepsy. I wasn't stopping there, but this is for the acute management and mind you, she is not pregnant right now and that had been checked. Essentially, we tried to choose a sodium channel. So, we're really just treating the seizures at this point. But with this abrupt onset behavioral changes, lots of seizures out of nowhere with no history of seizures, no prior really risk factors for epilepsy.

Dr. Stephen VanHaerents: 20:41 My suspicion that this is autoimmune-related is very high at this point. We start a more aggressive workup, started looking at her spinal fluid. And so, her spinal fluid really was fairly benign. It looked normal. She had one to two white blood cells, which is not uncommon. She didn't have any blood or red blood cells. Her glucose was normal, her protein was normal. She didn't have any signs of inflammation in the spinal fluid. And so, it was really kind of unremarkable, which is good. I mean, you don't want things to look really abnormal either, but it really didn't give a solid diagnosis of why she started seizing so quickly.

Dr. Stephen VanHaerents: 21:28 But remember we talked about this last time in the diagnostic portion that the CSF or spinal fluid that you get it from the spine, but it's really fluid that surrounds your brain and your spinal cord. And it can look normal. In fact, 25% of patients in

this study from, this was done in Quebec that they found that it was normal. Now, when you have oligoclonal bands that did increase the sensitivity to which hers was normal as well. Now going back on this patient that we kind of think about what should we do? You have a high index of suspicion that she has an autoimmune cause, but at this point, don't have anything definitive to kind of put your hat on, essentially, to hang your hat on. And so, when I think about it in this patient, that's usually when I start going for things like immunotherapy trial. And when you do immunotherapy trials or any treatment, let's just talk about how do we treat these.

Dr. Stephen VanHaerents: 22:37

And I tend to stick to the kind of the Mayo Clinic three M model. And while it might be kind of a silly thing to say, it's good to just keep this in mind that when you're giving anyone immune suppression, you want to do maximum reversibility. Your goal, in the beginning, is to get at least 50% of the seizures to reduce. And you have to keep in mind too, especially some of the intracellular more aggressive autoimmune encephalitis that you might not be able to reverse it, that some damage has already been done. And your goal really is to just stop any further progression. And I think that's an important thing to remember. And then you want to maintain that reversibility with the lowest therapeutic dose that you can. This is the biggest thing that I always emphasize to our trainees and when I give these types of talks to clinicians.

Dr. Stephen VanHaerents: 23:34

Because when you're going in a trial, especially in someone you're not a hundred percent sure if this is going to be autoimmune or not, you want to have very objective, as objective as you can markers to see if they have any response to the immunotherapy. The last thing you want is to say, "Well, before they seemed a little off and now, I guess they seem maybe less off." That's not really a great marker. You want to be objective. If you're talking about their cognition, I usually use a MoCA, which is the Montreal Cognitive Assessment Tool, which tests the brain's cognition in multiple different facets, or you can do a full neuropsychic evaluation if that center has that. When you're talking about seizures, you want to have seizure diaries if they're recognizing their seizures.

Dr. Stephen VanHaerents: 24:26

Now the patient we just presented; she really wasn't recognizing her seizures. She crashed the car and was having a convulsion, but had she not crashed that car, I don't know. I mean, she had five seizures on the EEG and no one was really noticing them. She's probably not a very good reporter. In this, you might want to get prolonged EEGs and see if you're making any sort of progress on the seizures. If their brain MRI is

abnormal, you can then follow the brain MRI, look for reduction of the inflammation. Maybe you're using the brain PET. Maybe they have a movement disorder, and you can see if it's progressing or getting better. Do they have autonomic dysfunction, something that you want to objectively follow though, essentially? And then you would start the trial. This is usually my treatment algorithm, and this is modified initially.

Dr. Stephen VanHaerents: 25:28

This is from the Mayo Clinic, which I've modified and Dr. Linnoila, who's a fellow at Mayo. She's now at Mass General had modified it. But this is typically what I do. I mean, there's always some nuance on a patient by patient and circumstances that might change how you try treat them. But this is kind of, if we're talking in a global sense, what I typically do. Let's go through it step by step, because this is a kind of overwhelming slide, especially if you're unfamiliar with a lot of these medications. If there's no antibody identified or you get one of these cells' surface ones like LGI1 or NMDA, then you typically go down this pathway, which you use methylprednisolone IV, which is a steroid, which is going to just bring down inflammation globally. It's not necessarily targeted at anything.

Dr. Stephen VanHaerents: 26:24

IVIG is Immunoglobulins that are concentrated when you give blood, your blood is separated into multiple parts, so you have red blood cells, and then you have clotting factors. You have platelets. But one of the other things they take when you donate blood is an immunoglobulin. So really this is donor antibodies. Another thing that you can do is plasmapheresis or abbreviated PLEX and this is essentially where you're hooked up to a machine and your blood is essentially being washed of protein, which is trying to get your bad antibodies out of your blood. In this particular patient, so then you usually try one of these, and usually, you start with steroids, unless there's some big contraindication to it like they have uncontrolled diabetes, because it can mess with your glucose, something like that. And you do a trial. Now, if you're inpatient and they're very unstable, like they're still having lots of seizures, at that point you're probably going to go to kind of a bigger gun.

Dr. Stephen VanHaerents: 27:28

Then I'll use something called rituximab, which is a monoclonal antibody. So, it's an antibody that you are giving them directed against the ... Remember we talked about the two branches of the immune system, the B cell line. This is really good for those cell surface antibody ones because you're blocking the development of those plasma cells. If it's undifferentiated or if it's intercellular, you might want to use something called cyclophosphamide, which is a chemotherapy drug and is aggressive. And so, you also, you don't want to just give this out

freely and you do need to discuss with patients about fertility consequences and things that can happen when you're using these types of drugs.

Dr. Stephen VanHaerents: 28:17

And so after essentially if they're continuing to be sick. Now, if they're outpatient relatively stable and you have a high index suspicion and they didn't seem to improve on one, it's not unreasonable to try another one, but that's really a case-by-case basis. Now if they improve. If you give a patient a thousand milligrams of steroids for three to five days, and then they start improving well, great. Their seizures controlled, you have those objective markers, and they start getting better, then that's awesome. But remember we kind of talked about then you have to kind of figure out, does this person need long-term immunotherapy? Remember we talked about autoimmune associated epilepsy versus acute symptomatic seizure or secondary to autoimmune encephalitis. Some patients just will have seizures and related to the brain information, but it's a monophasic single event and they can be slowly weaned.

Dr. Stephen VanHaerents: 29:17

So what I typically do is then I slowly start to taper it over months. If let's say they responded to five days of IV steroids, then I'll pulse them with one gram, usually weekly for about six to 12 weeks, depending on the severity and the time needed to recover. And then I'll start spreading it out. So, like every other week, every third week, and then monthly. And at any point during that time you're tapering, they start relapsing. Hold on one moment. Sorry, someone was knocking on my door so I just muted one second.

Dr. Stephen VanHaerents: 30:02

Sorry about that interruption. Okay. Then you slowly start weaning over time and see if they get better. I mean, you're looking to make sure that they don't get worse, essentially. If they do get worse, then they've kind of declared themselves that they need more long-term immunotherapy to which then you might start pulsing them again and then giving them a long-term medication. For instance, rituximab that we had talked about or mycophenolate azathioprine, these are two pills that you have to base on the individual antibody and the side effect profiles. But at this point, you know that they need something long-term. Now, if there's no relapse, then great, this is maybe a monophasic thing and then they just keep on going. Now we don't fully know the risk of relapse of each individual patient. We do have some data over time but keep in mind, we're discovering new antibodies all the time, which doesn't leave a long time to have long-term follow-up.

- Dr. Stephen VanHaerents: 31:11 For instance we discovered NMDA antibodies in 2007, and that's probably one of the best-studied and that's not that long ago to have that long of follow-up. We really don't have great data on how long to treat and what the risk of relapse if it was monophasic. So, it's important to keep that in mind. Oops, always you want to look if there is a tumor and if there is a tumor and if it's intercellular, you have a high index, a suspicion for say, you really want to continue to screen for a tumor because you might be missing it and it might be very small. So, you aggressively look, I usually do surveillance for up to five years. Now, if it's an intercellular antibody-like anti-hu, very aggressive. At that point, you start IV cyclophosphamide usually, which is very aggressive.
- Dr. Stephen VanHaerents: 32:12 Remember we talked about that, but this antibody, their brain just starts, they get damaged so fast that you have to be very aggressive off the bat. Usually, you pulse this for about six months monthly and these patients can often pass away. This is very aggress. You have to be very aggressive with your immunotherapy. And that's essentially kind what I do. And like I said, I gradually extend the steroids or IVIG depending on what improved. I try not to use oral prednisone, which is the oral version. A lot of these patients are very agitated already and so it's hard for them to tolerate the oral, but if there's no access to any sort of infusion center, depending on where they live, live in a rural area but not a lot of access. Sometimes I do have to use oral prednisone.
- Dr. Stephen VanHaerents: 33:12 And if switching to long-term immunosuppressants, they do need an overlap with the steroids, which I always try to remind people as well, that they do need to likely be on two agents for a while. Like for instance, azathioprine can need up to like 12 weeks until it's really effective. And then you may need to continue these long-term. But like I said, we really don't have a lot of data to guide us how long we actually need this long-term immune suppression. Even with bad NMDA receptors and encephalitis, sometimes I will try, for instance, I just had a young woman that wants to try for pregnancy off immune suppression. And so, she had been doing extremely well and been over two years. And so, we've tried to wean her on immune suppression and thus far she's been doing great.
- Dr. Stephen VanHaerents: 34:08 Some people can be weaned later too. Caveats to treatment. It's important to note that the presence of an antibody does not all always guarantee a good response to treatment. This especially true when there is paraneoplastic antibodies and/or intercellular antigens. And I would love to say that all my clinic patients have done amazingly well, but recently over this past

December one of my patients had anti-hu encephalitis, and it was very aggressive, and it left her brain where she was minimally verbal. It just attacked her brain so bad. And she had made her wishes very clear that she wouldn't want to live in any facilities or have assistance. And so eventually her daughter essentially, they made this decision which was easier for them because she had made her wishes known to put her on hospice.

Dr. Stephen VanHaerents: 35:10

And so some of these can be very aggressive and even when you hit them with cyclophosphamide like we were, we were very aggressive off the gate. Sometimes the damage to the brain is so severe that maybe even though they necessarily they survive, it might not be a place that they wanted to live in either. I think there's a lot of ethical considerations can also come about when you're talking about these types of treatment. And like I said because sometimes successful treatment might just be stopping any further progression, but you can't undo the damage to the brain that had already been done which was the case in that patient I just told you about. And it's also important, especially cognition can take months to fully recover, sometimes years really. Seizures usually show earlier improvements four to six weeks, sometimes up to 12 though, but cognition tends to recover more slowly. Just keep that in mind too.

Dr. Stephen VanHaerents: 36:18

And about 20 to 50% of patients with autoimmune encephalitis showing adequate response to even second-line therapies and will have persistent neurologic issues. There was a case that they wrote an article about, which is also the media release that we used bortezomib on a patient, which is actually a drug designed for multiple myeloma. And so sometimes when you have very aggressive, very aggressive cases, you can try some of these. Tocilizumab is another more novel agent, which is actually blocking something called Interleukin 6. And so that is an inflammatory cytokine. And so, there's other available treatments. I only really show this that it's not limited to that algorithm that I showed you initially that sometimes you have to think outside the box. Essentially, that is kind of the standard algorithm for most patients. And I wanted to emphasize too, just early treatment is better and that seizure meds alone don't seem to hold these patients.

Dr. Stephen VanHaerents: 37:28

So this is essentially looking at faciobrachial dystonic seizures. And we looked at this last time of [inaudible 00:37:36] drugs alone and then [inaudible 00:37:37] drugs with therapy. And then this is really concerning that the delay looking at the odds of getting control of these seizures, and this is the delay of starting immunotherapy. The longer you delay, the less likely

you will get control of the seizures. It's important to kind of keep that in the back of your mind as well. Going back to our patient, in that workup, she had an unremarkable ultrasound, although interestingly, it did look like she had a menopausal uterus essentially at that time. And her TPO antibodies, her thyroid antibodies were very high, which are kind of markers of autoimmune disease, but not necessarily specific in any way, but given the high index of suspicion and presumed autoimmune epilepsy, we did give her five days of steroids in the hospital and IVIG and she was discharged after nine days with resolution of seizures and she had vast improvement in behavior and she was discharged on slowly steroids.

Dr. Stephen VanHaerents: 38:51

It did come back eventually. It did take about 10 business days to come back, but she did have anti-voltage-gated potassium subtype to LGI1, actually quite high titer in the blood. And so she did have a positive antibody, but by the time we got that back, she had already been started on treatment, was actually doing much better, and the nice thing so she was then placed on lamotrigine over eight weeks and we weaned off the phenytoin and then slowly she was weaned on pulse steroids and then she did get some IVIG for titers in her blood of the voltage-gated potassium did go down, but I never rely on titers alone because they can be inconsistent and you really want to go off their symptoms more. And then she was weaned off steroids. This ended up being monophasic and she really has very little memory of this entire thing.

Dr. Stephen VanHaerents: 39:46

And she's totally back to normal, doing great. It was just one of those things. Her husband is very grateful. Before all of this, he was considering divorce. There was a lot going on socially and so now she's just back to the way she was, and she's not on seizure meds and she's not on any immune suppression at all anymore. That was essentially the talk on therapies. And if you have any questions, let me know, and then I have the citations as well on the talk.

Laura Lubbers: 40:24

Great. Thank you, Dr. Vanhaerents. That's a great way to end the story of a positive outcome for that patient and the challenges that she and her family went through. Truly a difficult story, but one that had a good outcome and wonderful to be involved with I'm sure. As you know, we do have an audience that is full of questions and so I just want to encourage everybody to please put your questions in the Q&A tab on the Zoom panel and click send, and we will work our way through as many as we can. We do have some appreciation in our chat for the talks. Thank you for that. And one question, has there been success in diagnosing and/or treating somebody

with a longer history of epilepsy and autonomic dysfunction?  
Treating early is good.

Dr. Stephen VanHaerents: 41:20

Early is good. This happens where the diagnosis of an autoimmune cause is made much later than desired. And at that point, I usually do do a trial, but sometimes they don't respond, there's damage done, and they have persistent epilepsy for instance. And then I still look, is there any component of it that's still immuno responsive or do they just have a structural epilepsy at this point due to damage from the brain? And so, I do try to still tease that apart to see if there's any immuno responsive component left, but often, not often. I mean, it depends case by case, but there are many that there's no further immune component but they do are left with a structural long term epilepsy. And then they kind of go down more of what you think of for standard epilepsy and maybe you think about epilepsy surgery or neurostimulators, things like that.

Laura Lubbers: 42:23

Okay, thank you. Here's a question that I hope I'm interpreting it correctly. And I was curious about it too when you were talking about the plasmapheresis approach. You're clearing the blood of the bad antibodies but aren't they going to come back. Won't they regenerate and if so, what do you do?

Dr. Stephen VanHaerents: 42:41

Right. This is an acute treatment that you're doing, it's not a long-term maintenance therapy. When you're dealing with someone like NMDA receptor encephalitis that antibody is toxic. If you take it from one mouse without NMDA receptor and encephalitis and put those antibodies in the other mouse, they will become symptomatic. And those intercellular antibodies, not so much. You want to clear the blood to get them out. And so, you clear it, but long term, often we use something called rituximab, which then is an antibody then directed at the bone marrow to stop making. So, you don't differentiate into those plasma cells, those progenitor plasma cells so you stop making the antibody. But that's a great question. And you also want to be sure not to give the rituximab before the plasmapheresis then you just wash out your very expensive therapy either. You wash the blood first.

Laura Lubbers: 43:40

Okay. Thank you. Considering that autoimmune encephalitis due to ... And you know our audience, they're very sophisticated here. Considering that autoimmune encephalitis due to LG1 is associated with hyponatremia. I was wondering whether it's better to treat with carbamazepine or could we use other sodium channel blockers like lacosamide if they don't want to use.

- Dr. Stephen VanHaerents: 44:03 That is a great question. And I would not use carbamazepine in someone with hyponatremia and for the audience who doesn't understand why that question was asked is carbamazepine or oxcarbazepine, that family really is associated with low sodium. And so, you're right. I would probably use something like Vimpat now keep in mind Vimpat's not benign. Oh, sorry. I probably should use generic names, lacosamide, sorry. Lacosamide. But some of these patients have autonomic dysfunction too. And so, you do want to really monitor these patients' parts too. Some of these sodium channel blockers a lot of them can either prolong QTC intervals, which you have four chambers of the heart, and the PR interval is how long it takes from the smaller atrium to get to the ventricles. And so essentially you want to monitor their heart too. When you're looking at that study, you have to take it with a grain of salt. Yes, and LGI1 carbamazepine did it better, but you have to think about the patient too. And so, what's best for them at that moment.
- Laura Lubbers: 45:19 Okay. Very complicated algorithm there to try to sort through.
- Dr. Stephen VanHaerents: 45:23 That's a very [inaudible 00:45:24] question.
- Laura Lubbers: 45:27 Yes. As always. You covered a lot of this in your first webinar and for those of you who are interested in seeing that it is on our website so please go to our website, check out our archived webinars for the webinar that Dr. Vanhaerents provided to us last month. And you've given us the example of this woman who's experienced real changes in behavior, some inconsistencies, but what other things might tip off family members that might be a cause for concern for autoimmune epilepsy. How do you trigger epilepsy investigation?
- Dr. Stephen VanHaerents: 46:15 That was in my first talk of kind of what are autoimmune seizures like as opposed to other seizures and keep in mind that patients with epilepsy, depending on the location of the epilepsy might have a lot of psychiatric comorbidities related to their epilepsy much higher risk of anxiety, depression, other things. Not everyone with any sort of psychiatric comorbidities autoimmune. I just want to give that kind of caveat off the bat, but the seizures of themselves are typically location-wise. And this is where talking to your doctor is important too, this kind of perisylvian, these kind of autonomic type seizures of the insula and areas and they tend to often be very brief seizures where you can have lots per day. No, when you look at this patient I just presented, she went from never having a seizure, you to having tons of seizures, tons, and they're very short and brief, and they tend to be very medically refractory off the bat.

- Dr. Stephen VanHaerents: 47:24 That's not typical of most epilepsies, unless it's a genetic epilepsy from a young age where they can be very refractory very early. This 27-year-old to develop that refractory of epilepsy in the course of a couple months would be very atypical. And then bilaterality too like having seizures like the guy last time I showed you, he had got left temporal seizure, right temporal seizure, left temporal, like having refractor. And he was 60 something. I forgot his exact age, but refractory epilepsy in a 60 something-year-old bilateral, that's really hard, and older people with structural epilepsy, usually, it's from a stroke or maybe they had a brain tumor and it's from one spot. Maybe it propagates different so they can have different seizure types. Let's say it's in their parietal lobe and sometimes it will go backwards and they'll get a visual aura or sometimes it will go forward, but they have from two different sides that refractory that should really raise your index of suspicion. Something is up here. There might have been too complex an answer.
- Laura Lubbers: 48:37 Well, I think it's really important for families to recognize these different behaviors. We think about so much of the public thinks about seizures in a specific way. And they don't associate seizures with this kind of abnormal behavior or even anxiety. I think DeJa'Vu is underappreciated so I'm glad you brought that up as well. And that there are different things that might indicate this and to go to a clinic and get a good workup is critical and certainly don't dismiss the person and what they're experiencing. Try to find a root cause for that and address it.
- Dr. Stephen VanHaerents: 49:17 Even if it's not autoimmune, I just want to say, it's not like I only see autoimmune epilepsy patients. I have plenty of other epilepsy patients too structural and infectious causes metabolic genetics, but it's important I always screen for mental health and treating. It's the same brain. They're not so much separate as you need to also treat the mental health aspect too. I don't want you to ignore, oh, well they're not autoimmune or whatever, you don't have to think about psychiatric comorbidities, but psychiatric comorbidities and epilepsy should always be addressed.
- Laura Lubbers: 50:00 Right. And this makes me think also of a webinar from last year in case people are interested on the issue of non-epileptic, psychogenic non-epileptic seizures, which has a very similar feel to this in a way.
- Dr. Stephen VanHaerents: 50:13 Right. I'm glad you brought that up because they often can also have a very abrupt onset where they seem very refractory to medications. The big differentiator there is when you put them on EEG, there is no EEG correlate. But sometimes you are

absolutely right, the presentations can actually look very similar. And that's why the workup is important.

Laura Lubbers: 50:43 Right. And bringing in the workups for the mental health as well as other forms of epilepsy. It's critical. Really broadening our vision of epilepsy here which is wonderful. Here's a question that came up after last month's webinar, which is related to the titration of epilepsy medications. And so if typically somebody presents what seems like a seizure and they get put on a standard anti-epileptic drug, but then in the workup, it's determined that, well, perhaps they actually have an autoimmune epilepsy and they go through that process. You've described it in your patient that you just presented to us where they titrated off of the immunotherapy and also for her off of the AEDs but that's a very scary proposition for many to think about coming off of the anti-epileptic drug completely. How do you make those decisions and how do you work through that process?

Dr. Stephen VanHaerents: 51:50 This is how I usually do it, which is not always a hundred percent standard. And I'm glad actually now I didn't even think about it, but those two cases, the case in the first one, he was unable to actually come off seizure meds. And I think that part of that reason I believe is that in the first case, he really presented it in September, but I didn't meet him until March or April. So, there's a large delay. And one rule of thumb so you do him second, we'll talk about the patient I just presented first where she was able to come off both. Her cognitive seizure had all stopped really by about eight weeks at that point. She responded very quickly, which is awesome for her and we also got to her very quickly too.

Dr. Stephen VanHaerents: 52:41 So she really wasn't that symptomatic without treatment very long. So essentially what I do is I never wean seizure meds and immunosuppression at the same time, because then if they have a breakthrough seizure, you don't know is it because they have structural damage that now they have epilepsy or is it that they're having a relapse of their autoimmune encephalitis and need immunotherapy. So, I never wean them at the same time. So, in her, I slowly wean immunotherapy while I kept her seizure medications stable. At which point when she's off immunotherapy doing great, I usually get a follow-up EEG. Does she have any sharp waves or any epileptic potential whatsoever? At this point in her, she really can't be driving anyways because it's still within six months.

Dr. Stephen VanHaerents: 53:31 She wasn't driving. And I discussed with her seizure, precautions risk. I usually give them at home rescue too, in case they do

have a breakthrough seizure. And I educate the family, seizure precautions, things like that. And then we slowly wean off and then once weaned off, I usually do a follow EEG to make sure that there's no epileptic potential in her there wasn't, but really we don't have a perfect marker to mark someone's epileptogenicity and that's an area of research that, for another webinar, you might want to invite [inaudible 00:54:04] from Beth Israel at Harvard Medical School who's looking into that and has some great data. But anyways, right now we have a limited approach.

Dr. Stephen VanHaerents: 54:12 I think essentially that time is really the best marker. The longer you can go without seizures. And so, in her now it's been six-plus years without a seizure. So, she's doing really well. The other guy, when I weaned him, actually he got off immunotherapy. He was doing great. But when we did the follow-up EEG, he still had epilepsy from discharges, from his temporal lobe. With him, we discussed any potential wean, but in him, he didn't feel that it was worth the risk. He also took longer to recover. So, it was also over six months. And so, he was driving again, which is also a big consideration as well. So, it's really a case by case and discussing with them the different options. I hope that answered that question.

Laura Lubbers: 55:12 I think that's terrific. I think that gives us some really good examples of which direction to go and why. Thank you for that. I think we have time for one more question, and this is interesting and very relevant to today. Can you speak to how patients have experience any changes or flareups in autoimmune epilepsy following COVID infection and any protocols you recommend for these patients?

Dr. Stephen VanHaerents: 55:39 Presenting for the first time after COVID or they already had autoimmune disease and then got COVID?

Laura Lubbers: 55:44 Sounds like they already have autoimmune epilepsy, but I'd be interested in the first scenario.

Dr. Stephen VanHaerents: 55:49 The reality is both. I've seen it flare up from both. I mean, the reality is if you kick up the immune system, even with just and by no way am I anti-vax, but with the vaccine, I've seen upticks too. You're activating the immune system if they make autoimmune antibodies, it makes sense. The vast majority of my patients have been totally fine, to be honest. I didn't know how that would happen, but there are a couple notable ones that it did kick up. And in which case I've treated them just like I would. Anyways, I gave them steroids in those cases to bring down inflammation. I just treat it essentially. But luckily it hasn't

as bad as I initially was concerned and a lot of us were concerned about when the pandemic first started.

Laura Lubbers: 56:51 Yes, I'm sure. And I think that actually addresses another question with what's the risk of recurrence and how do you treat it? And it sounds like you treat with steroids.

Dr. Stephen VanHaerents: 57:01 Yeah. I mean, so it also depends too. I took an NMDA receptor encephalitis patient off rituximab which had worked for her for years when she relapsed, I did give her steroids actually, but then I gave her rituximab to go back on it too. It depends. If there's something that was working for them before it's got taken them off, then you restart it.

Laura Lubbers: 57:24 Right. Okay. Well, I think we are at time and I want to thank you again for a very engaging presentation as always. I also want to thank our amazing audience for all your terrific questions. We can always count on you to bring thought-provoking things to these discussions. Thank you to all. If you have other questions, please do send an email to us. If you want to learn more about CURE Epilepsy research programs, you can do so by visiting our website. Again, our email address in case you're interested is [research@cureepilepsy.org](mailto:research@cureepilepsy.org). And finally, please stay tuned for the announcement of our April and May webinars, which will be coming out soon. Once again, thanks to all and be well.