CURE CITIZENS UNITED FOR RESEARCH IN EPILEPSY

THE EPILEPSY-AUTISM CONNECTION: RESEARCH, DIAGNOSIS, AND TREATMENT (WEBINAR TRANSCRIPT)

Dr. Laura Lubbers: 00:01 Welcome everyone to today's webinar. I'm Laura Lubbers, and I'm the Chief Scientific Officer for Citizens United for Research in Epilepsy, or CURE. I want to thank you all for joining us today.

Dr. Laura Lubbers: 00:12 Today's webinar is entitled The Epilepsy-Autism Connection: Research, Diagnosis, and Treatment. It will explore the incidence of epilepsy in autism, why epilepsy and autism are so frequently connected, and the potential underlying biological mechanisms that might link the two.

Dr. Laura Lubbers: 00:31 This webinar is a continuation of our Leaders in Epilepsy Research Webinar Series, where we highlight some of the critical research that's being done on epilepsy. Today's webinar is being sponsored by our friends at the BAND Foundation.

Dr. Laura Lubbers: 00:45 CURE's mission is to find a cure for epilepsy by promoting and funding patient focused research. CURE has been instrumental for over the past 20 years, by supporting groundbreaking research projects from around the world. When applicable, at the beginning of each of the webinars this year, I want to spotlight research that's being performed by one of our CURE grantees in a related area of epilepsy research. Today's spotlight features Dr. Daniel Barth, a 2016 CURE epilepsy award grantee.

Dr. Laura Lubbers: 01:18 Dr. Barth and his team of investigators discovered that suspected environmental risk factors for autism, such as maternal stress, and certain common prenatal drugs only when combined, produced autism-like behavior and epilepsy in offspring. These combinations also resulted in marked brain inflammation, a reaction of the immune system thought to contribute to both epilepsy and autism. They developed an animal model of epilepsy in autism, to study the effects of combined environmental inflammatory factors to establish human maternal guidelines and to explore the anti-inflammatory strategies to prevent or reduce the

severe neurological syndrome. For more information on this specific project, or other advancements being made by CURE funded researchers, please visit our Epilepsy News section of our website.

Dr. Laura Lubbers: 02:13 Today's speaker is Dr. Jamie Capal, who is an Associate Professor of Pediatrics and Neurology at Cincinnati Children's Hospital Medical Center. Dr. Capal has been an integral member of the multidisciplinary Tuberous Sclerosis Complex Clinical Center of Excellence and maintains a busy practice, diagnosing and treating children with autism spectrum disorder, and associated neurological disorders.

Dr. Laura Lubbers: 02:41 Her current research is focused on the area of autism spectrum disorder and tuberous sclerosis complex. Before Dr. Capal 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 at the bottom of your ZOOM panel and then click send. I also want to thank those who already submitted questions for this webinar. We will do our best to get through as many of the questions as we can. We do ask, or we do want this webinar to be as interactive as possible, but to respect everyone's privacy, we ask that you make your questions general and not specific to a loved one's epilepsy or autism. I also want to mention that today's webinar, as well as all of our previous and future webinars will be recorded and are available on the CURE website. So with that, I'd like to turn it over to Dr. Capal.

Dr. Jamie Capal: 03:41 Thank you for having me. I am going to speak about the epilepsy autism connection today. So there's a lot of things I want to cover, but I will try my best cover as much as possible on this very important topic. Really no relevant disclosures for this talk today.

Dr. Jamie Capal: 04:09 So my outline, I'm going to speak about epilepsy in autism spectrum disorder, and then I'm also going to speak about the converse, autism spectrum disorder in epilepsy. Then I'll talk about the connection between autism and epilepsy, and then also discuss a little bit about autism and abnormal EEG findings. And then finally, how to evaluate epilepsy in the setting of

autism spectrum disorder and future directions for research.

Dr. Jamie Capal: 04:41 So autism spectrum disorder, just for those of you who aren't familiar with the definition, is a neurodevelopmental disorder that affects social communication and restrictive and repetitive interests. It's currently behaviorally defined as a DSM 5. There are many, many causes for autism spectrum disorder, and also no one treatment that treats the disorder.

Dr. Jamie Capal: 05:16 This, although blurry, shows you a little bit about some of the many comorbidities in autism. As you can see, there are difficulties with sleep and mood, many neuropsychiatric disorders: Anxiety, ADHD, aggression, also intellectual disability. But what I want to show you is that seizures is one of many of the comorbidities of autism, and that's what we're going to focus on today.

Dr. Jamie Capal: 05:45 Epilepsy, just to review the definition, is characterized as a brain disorder, characterized by a predisposition to generate epileptic seizures. About one in 26 people will actually develop epilepsy in their lifetime, and there are several risk factors for development of epilepsy. One of the biggest is intellectual disability, but also any kind of brain abnormality, so traumatic brain injury, congenital malformations, history of stroke. There are certain genetic mutations that increase your risk for developing epilepsy, and also a history of brain tumors and infections can also increase the risk of developing epilepsy.

Dr. Jamie Capal: 06:28 So, first I want to talk about epilepsy in the setting of autism spectrum disorder. The research is obtained by various methods but overall, we know that there's a higher risk of developing epilepsy in the setting of autism. Roughly about one third of patients with autism can develop epilepsy, but the research has shown anywhere from two percent to 46 percent. Much of that is based on how they collected the data versus population data or the research clinic. But we do know that there is a much higher percentage. We know that there's a bimodal age of onset, so epilepsy is more common in very young children, and also in adolescents and young

adulthood. Research has shown that up to 20% of individuals with autism that are going to develop epilepsy develop it in adulthood. There are no specific seizure types. It's pretty much the same as any other type of epilepsy. And then no specific epilepsy syndrome associated in individuals with autism.

Dr. Jamie Capal: 07:39

So I'm going to talk about a little bit about the associated factors that may increase your risk of epilepsy in the setting of autism. One of the big ones is age of seizure onset. Like I said, as you get older your risk of having epilepsy in the setting of autism increases. So, this is a big study that looked at four different collections of individuals. Some of them were research studies, some of them were population based studies, parental surveys, and what this is showing is the average prevalence of epilepsy. So in the younger kids, it was lower but it was still at 12%, was the average prevalence throughout. And then that prevalence reached 26% by adolescence. So as you can see, even though these are collected from all different individuals, we do know that as they get older, more and more individuals will develop epilepsy. We also know that this study also looked at intellectual disability, which is another risk factor that we're going to talk about in a moment, and for every increase in your IQ, your standard deviation in your IQ points, the odds of having epilepsy decreased by about 47%.

Dr. Jamie Capal: 09:05

The other big factor is intellectual disability, and it's currently defined in different ways, but the way the paper defined it was an IQ of less than 70, with adaptive behavior deficits. And this paper looked at... It was a meta-analysis assessing the risk of epilepsy in autism, according to intellectual functioning, as well as gender. And so as you can see here, as your IQ decreases, your epilepsy rates increase. What they found that the pooled prevalence of epilepsy was 21.4% in the autistic individuals with intellectual disability versus 8% in the autistic individuals without intellectual disability. So although we know that the lower your IQ the higher the risk of epilepsy, even those without intellectual disability had a much higher risk for developing epilepsy than individuals in the normal population.

Dr. Jamie Capal: 10:06 Another associated factor is gender. There have been conflicting studies that show gender differences as it relates to epilepsy. Many think that females are at an increased risk of developing epilepsy versus males. So there's a couple studies that looked at this question. The same meta-analysis that I just spoke about, also looked at gender and they did find that females had a higher incidence of epilepsy compared to males, so the ratio, when you just look at individuals with epilepsy, was actually close to 2:1, versus about 3.5:1 in individuals without epilepsy.

Dr. Jamie Capal: 10:47 The other study that came out showed that looking specifically at females with intellectual disability, and refractory epilepsy, it showed that females with refractory epilepsy were more prevalent than those without treatment-resistant epilepsy. They also found that the actual symptom severity of autism was lower. And some of the theories in this paper look at... The thought is that females need a much higher genetic burden in order to develop autism.

Dr. Jamie Capal: 11:25 And so, we see a lot more comorbid neurodevelopmental conditions when you see females with autism and epilepsy, versus males with autism, because they just don't need as much of a genetic load. And that theory is still being looked at, but it is something to think about when we really are thinking about the differences in gender.

Dr. Jamie Capal: 11:50 Other factors to think about are family history. Some people have seen that if you have a family history of epilepsy, those individuals also have an increased risk of autism in other family members. So what this means is that epilepsy and autism likely have common genetic factors, that if you have someone in your family with one or the other, that your risk for having either one in other family members is higher.

Dr. Jamie Capal: 12:22 We also know that genetic syndromes like the neurodevelopmental genetic syndromes of Fragile X, Tuberous Sclerosis Complex, and Angelman syndrome, just to name a few, have higher incidences of autism, intellectual disability, and epilepsy. And so really research is focusing on these neurodevelopmental conditions to allow us to understand the underlying mechanisms of autism and

epilepsy and intellectual disabilities so that we can understand exactly how these are playing together and then develop treatment targets.

Dr. Jamie Capal: 12:56 We also know that neurologic abnormalities can increase your risk for epilepsy and autism. Then there's a lot of question about regression in epilepsy. Many people who come to the neurologist to look at regression, they often will get EEGs to rule out any sort of epileptic encephalopathy that might be causing autistic symptoms. The research is conflicting when it comes to regression. I do have a slide coming up on that in just a moment. When we think about regression in autism, about a third of individuals with autism spectrum disorder exhibit developmental regression, typically that's between 18 and 24 months of age. And so people are really interested in if there is a link.

Dr. Jamie Capal: 13:48 Some research suggests that epilepsy is a cause of autistic regression, while other people look at it as not a cause of regression. There have been other studies that look more specifically at the epileptic abnormalities, not necessarily epilepsy, but just abnormalities on an EEG. And certain studies have found that those are more frequent in regressed children, so it's hard to know whether this is a causative thing, or just an associative factor. Or we're biased because currently EEGs are not standard to do on everyone with autism, so are we biasing those individuals that we are actually doing EEGs on? So, we don't really have a great idea of if this is something that's seen in the entire autism community, or just part of the autism community.

Dr. Jamie Capal: 14:44 Next I want to talk a little bit about the frequency of autism in epilepsy. So, we know that rates of autism in epilepsy are higher. These rates are anywhere from 5 to 37%, and again, it really is a function of how you run your studies, and that's why the rates are so variable. We know that this is again, strongly associated with intellectual disability, and the lower your IQ, the higher your risk of having autism in the setting of epilepsy. This risk has been shown to increase with a history of infantile spasms. So, that is something that people are looking into, and following out individuals with infantile spasms. Certain genetic

syndromes, like I said before, also have a higher prevalence of autism spectrum disorder.

Dr. Jamie Capal: 15:42 Important questions that I was thinking about as I was making this presentation are, what comes first, is it the atypical development, or the epilepsy? Are there underlying brain mechanisms that predispose an individual to having both? Can we identify specific behavioral, and developmental characteristics in children with autism in epilepsy, particularly in the setting of comorbid intellectual disability that provide insight into potential therapy? And also, in light of epilepsy, and autism, both being such heterogeneous conditions, is there a distinctive ASD/epilepsy phenotype? The reason I think about that is because if you think about both conditions, very hard to study both of them if you just take a blanket approach, but if you look at them based on their comorbidities, is this a specific phenotype that we can look at and develop treatments?

Dr. Jamie Capal: 16:53 So, this paper looked at... It's a big prevalence study in a Norwegian patient registries, 700 thousand patients. What they found was that 11% with autism had epilepsy, and then 6.1% of children with epilepsy had autism. So, then I think the big question is, is there a causal relationship, or are epilepsy and autism the result of the same underlying mechanism? The way I've been introduced into this field, and one of the ways that we've studied this is through our syndromic autism spectrum disorder. Which, syndromic autism just means autism that's also associated with epilepsy, and intellectual disability. Often these have a genetic cause.

Dr. Jamie Capal: 17:44 So, one of my specialties is studying tuberous sclerosis complex. Tuberous sclerosis has a very high prevalence of autism, epilepsy, and intellectual disability. The mechanism is very well known. These patients are often diagnosed prenatally, or early in infancy so it's a perfect population to study prospectively, which is very difficult when you're thinking about epilepsy and autism. There have been a few studies that I just want to show you that are looking at this relationship between all three to really understand how they're related.

Dr. Jamie Capal: 18:26 A group out of UCLA started looking at this question several years ago, and what they did was they took 40 children with tuberous sclerosis ages 3 to 36 months, and followed them out prospectively. 55% of these patients were diagnosed with autism, and 95% were diagnosed with epilepsy. And this first paper really looks at, can we determine early on in the first year if there is anything that separates these two groups? And, what they found was at six months there were some nonverbal delays in development. So, in fine motor, and visuospatial skills in these kids that eventually went on to be diagnosed with autism. And, by 9 months the kids with autism actually had delays in all areas of development.

Dr. Jamie Capal: 19:15 The same group has looked at not just development, but also looked at the differences between tuberous sclerosis in the setting of autism, and autism for other causes. I didn't have enough time to show you all that, but what they found was that a lot of the symptom profiles were the same, and so this is another reason that tuberous sclerosis, and potentially other single gene disorders are great ways to study the development of autism, and how it affects the brain because they're very similar in their clinical presentations.

Dr. Jamie Capal: 19:59 The same patient cohort... Basically, what she found was that by 12 months of age, the children that were later diagnosed with autism, demonstrated significantly greater cognitive delays with declines in their IQs from 12 to 36 months. This was done on the Mullen Scales of Early Learning. But, as you can see that those who developed autism really pulled further, and further behind their peers, compared to those who did not develop autism. And so, a group that I've been particularly involved with, and this was the paper that we put out a couple of years ago, was really looking at the effect of seizures on development in this group of individuals. And so, what I'm showing you here is the Mullen Scales of Early Learning, which is a developmental scale for young children, and at the top... So this is a multidisciplinary study from five centers across the US, really looking at a prospective study from infants, from birth to 36 months, looking at developmental testing, imaging, and high resolution EEG, to determine if there are

things that we can learn about the development of autism in this group of individuals. And then, look back and say, "Is there a biomarker?"

Dr. Jamie Capal: 21:24 This is just really looking at the development, and how seizures affect that. So, in the red are the patients with seizures, in the green are the patients that do not have seizures, and as you can see at six months they're relatively similar. Starting to pull away, but as you go through 12, 18, and then 24 months, the individuals with seizures really do lag behind in their overall development compared to individuals who never had a history of seizures. And in the bottom you can see the middle line is everybody, and then we split them apart according to who had seizures, and who did not. And this, what we graphed, was the early learning composite score, which is a total cognitive score from the Mullen scales, but of the subdomains of the Mullen's which is fine motor, and visual reception, and expressive, and receptive language all showed similar relationships in individuals with seizures versus no seizures.

Dr. Jamie Capal: 22:26 We looked also at infantile spasms, history of infantile spasms, frequency of seizures, and the same relationship was found through all of them. One of the things that I didn't show you was, even having seizures early on, so the earlier you have seizures, the worse it affects your development. And, in the next slide I'm going to show you how that affected autism symptoms. So, in this slide we looked at six separate assessments looking at autism. One was the autism scale for infants at 12 months, and the other one was the ADOS, which is the Autism Diagnostic Observation Schedule at 24 months. And, what we found were that people with seizures, or the babies with seizures, showed much higher characteristics of autism, autism behaviors, even as early as 12 months compared to those who had never had a history of seizures. This was also the case with infantile spasms, and also the case for higher seizure frequency.

Dr. Jamie Capal: 23:33 We are currently doing analyses on a more detailed look at seizures, and how they relate to development, and actual diagnosis of autism, because we carried this out to 36 months to see if this relationship holds true, and that data is still currently being analyzed

now. But still, that relationship is very robust. And so, the question is are there convergent pathways to all three of these? We think about common processes that underlie epilepsy and autism. Some theories about overexcitable brains having the imbalance between inhibition, and excitation. We also know that some genetic epilepsies impact synapse plasticity, and cortical connectivity which can in turn predispose the early developing brain to developmental delays, and abnormal development in their connectivity which can eventually lead to autism. Again, I keep stressing the underlying genetic syndromes really, especially in autism, can affect neuronal synapses, and that can also predispose you to having epilepsy.

Dr. Jamie Capal: 25:01 It's very difficult, I think, to really figure out what comes first. I think all these things are very interwoven, and so when we think about treatments, we are really trying to think about treatments for everything, and not just for one. Ideally, if we found one, then maybe that treatment will affect the other aspects of this. Something I became interested in a while ago, and published a few years ago was looking at the epileptiform EEGs in autism, and even not just if it's abnormal, slowing and things like that. We know that epileptiform discharges are seen in up to 60% of patients with autism in the absence of ever having seizure, at least in the studies that we know, a lot of this was done cross-sectionally, and not necessarily followed longitudinally. But questions I think about are, are these EEG abnormalities predictive of developing epilepsy? Are they indicative of worse behavior, or development? Do they have impact on the core features of autism? What is the significance of these abnormal EEGs on autism, or is it just really reflecting disorganized brain?

Dr. Jamie Capal: 26:22 The studies that have been done, really mainly look at things, either in a cross-sectional manner, there have been one or two studies that followed people out prospectively looking at those who had epileptiform EEGs as they followed them out through the years, much higher percentages of those people developed epilepsy. So, that's a question that we think about. Is there a biomarker that we can think about? Who is going to develop this? But as I stated

earlier, we don't do EEGs as a standard for everyone with autism, so it's really kind of a biased sample when we think about it with who we're collecting EEG data on with these patients.

Dr. Jamie Capal: 27:20 The paper that my group published in 2018, we really looked at the patients that we had diagnosed with autism in our developmental and behavioral pediatric division, and we had 443 patients, and I really focused on the ones that had histories of seizures, and/or EEGs. And I really looked at them at the time they were diagnosed with autism, and not necessarily if they developed epilepsy later, just at the time of their diagnosis. So, at the time of diagnosis, about 16% of these patients had epilepsy, and about 25% of them had abnormal EEGs, and never having had a seizure.

Dr. Jamie Capal: 28:07 But, what I found was that children with autism, and these abnormal EEGs actually looked more similar to those with epilepsy than those with normal EEG results in the settings of adaptive behavior, and the presence of these abnormalities, or epilepsy in the setting of ASD can suggest maybe some worse developmental function. Now this was very preliminary, and it was a retrospective study, but it really makes you think about where to put these abnormal EEG patients. If they are more closely aligned with those with epilepsy, what can we learn from them, or should we be doing something for these patients that could somehow prevent it, or at least follow them out clinically. Do they eventually develop epilepsy? Or did behaviors change? And things like that. There really isn't a consensus currently, but I think it's just definitely something that we need to study.

Dr. Jamie Capal: 29:20 And so, when we think about conceptualizing this relationship, there's three different ways you can think about it. One, in the green, thinking there's one etiology, and it's going to impact everything. So intellectual function, eventually developing autism, epilepsy, abnormalities on your EEG. Then you have your causative model where you have a etiology that causes epilepsy, that causes ASD. So, when you think about your epileptic encephalopathies probably that they directly cause one another. But then, in the pink,

you think about, okay, you have this etiology, and then it could develop epilepsy, or ASD, or intellectual disability, and then one of those in turn affects the relationship of the other, and so it's definitely more of a dynamic relationship, which is kind of the way I think about this currently because there are certain genetic conditions that could result in either one, or both, but sometimes maybe epilepsy comes first, or autism, or intellectual disability, or intellectual delay comes first, and they can negatively impact the other systems.

Dr. Jamie Capal: 30:40 When we think about studying these, and doing research, we really have to think about how these relate to each other, because it really is not a linear relationship. So, it makes it very difficult to try to tease apart what causes what, and in turn develop therapies. So, then when we think about how we evaluate epilepsy in the setting of autism, and there really isn't a consensus on how to do this specifically in individuals with autism. At this point, it's the same as individuals without autism. However, physicians should have a high index of suspicion, and counsel their patients on what to look for because we do know the risk of having seizures is higher. Videos are helpful, because often stereotypic behaviors and things like that in autism are difficult to tease apart, especially for someone who doesn't quite know what they're looking for, so having videos I find is helpful.

Dr. Jamie Capal: 31:46 Talked a little bit about EEGs before, so now the question is do you screen with EEG in the absence of suspicion for seizure? At this point we don't, because there isn't enough evidence to support doing this. So, at this point, we only use EEG if there is a clinical concern for seizure. And then if EEG is necessary, it is preferable to do an overnight EEG to capture sleep because we know that we are missing a lot of abnormalities if we are just collecting data from the awake state. Antiseizure medication should really be tailored individually to the seizure type, and the individual patient factors. There is really no specific antiseizure treatment just for kids with autism. Genetic testing is becoming more, and more highly recommended due to these shared mechanisms. So, microarray is a great place to start. There are definitely more panels that are coming out that look

for genes that are shared between autism, and intellectual disability, and epilepsy. So those are also things to think about because we know that these kids are more likely to have genetic causes.

Dr. Jamie Capal: 33:04 And then finally, thinking about future directions. Figuring out ways to distinguish which individuals with autism will go on to develop epilepsy may help us prevent it, or recognize it sooner, and treat sooner. Also, by studying these genetic disorders with high rates of autism, epilepsy, and intellectual disability, we want to understand the different biological pathways that are associated with these three things in order to develop preventative, and ameliorative treatments.

Dr. Jamie Capal: 33:39 So, with that, I'm happy to take questions.

Dr. Laura Lubbers: 33:44 Terrific. Thank you Dr. Capal. So, we'll now begin the Q&A session. Again if you have questions, please submit them in the Q&A tab located at the bottom of the Zoom panel. I know we got a number of questions already. Click that send, and we will get them, and we will do our best to get through as many as possible.

Dr. Laura Lubbers: 34:02 So, one question that I have is, you shared a lot of information about tuberous sclerosis complex, so can you talk about the information that we've gathered there, and how that might translate to other neurodevelopmental disorders? How do we do that?

Dr. Jamie Capal: 34:21 That's a great question. And I think that's why... So, currently what we've learned is that early on, the earlier your brain gets disrupted, so that can be seizures for example, that those other pathways of intellectual disability, autism, those things, you're at a much higher risk for overall disorganization of the brain by having seizures early on. And so, what we're trying to figure out is, is there other things that can tell us what else is going on from a structural standpoint, from an EEG standpoint? Because the goal is prevention.

Dr. Jamie Capal: 35:02 So, there are studies going on now, one they call the PREVeNT trial, looking at early seizure treatment in babies with tuberous sclerosis that have not had seizures yet, but just have abnormalities in their EEG. If

you treat that before the seizures come, will you get better results with development? And maybe better results as far as preventing autism? So, that study is just closing right now, so we are very interested to find the result, because really that's the next step. Really, many other neurodevelopmental disorders are also looking at similar things, and what we know is looking earlier is better. The earliest that we can try to advocate for prevention, the better off we are to disrupt these mechanisms that result in developmental delays, and autism.

Dr. Laura Lubbers: 36:00 Thank you. Along similar lines, you mentioned that EEG is not standard screening-

Dr. Jamie Capal: 36:07 Correct.

Dr. Laura Lubbers: 36:08 For autism. What sort of information would need to be gathered in order to make that more standardized approach?

Dr. Jamie Capal: 36:16 I think what we really need is a protective studies, basically doing screening EEGs on all kids that are newly diagnosed with autism, and then follow them out longitudinally. But the problem is that it's a very expensive and long study, but I really think it's something that needs to be done so that we have a true idea of what the percentage of kids with autism have abnormal EEGs, and what is their risk of eventually developing epilepsy? That will give us the evidence we need to say, "Everybody with autism needs to get an EEG as screening." Right now we just don't have anything.

Dr. Laura Lubbers: 36:59 Okay. Great. Thank you. So another question that's come in, is there a relationship between the level, or type of autism with a particular seizure focus in those with focal epilepsy? So, if there's epilepsy emanating from a specific area of a brain, is that person more likely to develop autism? Or perhaps be associated?

Dr. Jamie Capal: 37:23 A lot of people have looked at this. There is some evidence showing that maybe epilepsy in the frontal region of the brain, or the temporal region of the brain may predispose you to having autism, but it's not universal. There's some evidence showing that.

Dr. Laura Lubbers: 37:45 Okay. Okay. So, you sort of touched on this with the PREVeNT trial in a way to look at it, but is there evidence that autistic children can improve cognitively with increased seizure control? Has anybody looked at that?

Dr. Jamie Capal: 37:58 We are currently looking at that as far as with the same study that was looking at the natural history of the development of autism. We actually collect all the seizure diaries, and we are actually going to look at treatment to see if anyone's scores improved with treatment. There's also a group looking at the benefit of epilepsy surgery via that by improving seizures, increase development. Again, the goal though is to look early because if you were to look at a 10 year old, early development in the brain has kind of been set, so you have to focus on the young, young children. That is where the field is going right now. There is nothing that's come out of it yet, but that's we're looking.

Dr. Laura Lubbers: 38:58 Okay. Okay. Similarly, just your thoughts on this. We know epilepsy can impact cognitive function, and cause cognitive decline in a way that might make an adult look like they have some aspects of autism. Is this due to the seizure activity, or is there a way to protect the brain from that seizure activity?

Dr. Jamie Capal: 39:30 That's a difficult question I think to answer, because when you think about the epileptic encephalopathies for example. So, those are the patients who are having lots, and lots of seizures, and even when they're not having seizures, they're background brain activity is abnormal. And so really those connections are not allowed to form correctly, so you're really going to get a lot of cognitive impairment because of that. In those cases, by controlling the seizures, you would expect the up cognition would improve, in those cases. In other cases though, where it's not that way, it's less clear that... I think you have to sort of think about epilepsy is not causing it, it's just maybe two things are happening simultaneously, and epilepsy is just making it worse. So treating epilepsy may help, but it's not going to reverse it.

Dr. Laura Lubbers: 40:33 Another question. Are there links between epilepsy, autism, and Alzheimer's?

Dr. Jamie Capal: 40:48

That's a great question, and I know... I can't say that I know a lot about the literature with Alzheimer's, but I can say that there's a lot of interest in looking at the connection between Alzheimer's and autism because I think there are a lot of shared genetic mechanisms there. That is definitely something that I think needs to continue to be looked at as we do more genetic studies to look at, what are the shared genetic links between individuals with Alzheimer's and autism. But, yeah. They found that there's a lot of similarities in the connectivity of the brain in both of those disorders.

Dr. Laura Lubbers: 41:38

Another question. Many people with epilepsy, including those with autism, are not responsive to medications, and antiepileptics can cause disturbing side effects, mood, GI, anxiety, increased repetitive behaviors that worsen, what are your thoughts about the VNS, and more specifically noninvasive VNS that is not approved in the US as yet? Does it help with autistic behaviors at all?

Dr. Jamie Capal: 42:08

I like VNS, I think that there are some folks that it works very well with. I had one patient, for example, who I was thinking about doing a VNS on, but because he is so active, and his behaviors were so erratic, that he really wasn't deemed a good candidate for it. But I do have other folks who... Another individual that I'm thinking of, that really did well with VNS because this individual was having so many negative side effects with all of the antiseizure medications, and we really couldn't find a good balance with medication. So, I think it's definitely an option with individuals with ASD for sure.

Dr. Laura Lubbers: 42:56

Back to sort of the question around focal epilepsy, this more directed to TS. Are there any neuroanatomical relationships between tuber location, and the development of autism, epilepsy, or both?

Dr. Jamie Capal: 43:12

Yeah. They've been looking at that. There've been a couple papers that have mentioned... I want to say again, like frontal and temporal, but nothing that's absolute. I know that part of this study that I'm part of is we are doing high detailed MRI studies looking at where the tubers are, what the burden is, but we don't have a definitive answer for that yet.

Dr. Laura Lubbers: 43:39 Okay. Yes. The follow up to this question is, is there a relationship between tuber load? So, it sounds like that's being studied.

Dr. Jamie Capal: 43:47 Yeah. It's kind of indirectly, but there's a paper that, if it hasn't come yet, it will be looking at the connection between seizure severity, tuber load, and development, and there's sort of an indirect relationship between tuber load.

Dr. Laura Lubbers: 44:03 Okay. Interesting. A more general question. Should all children diagnosed with epilepsy, especially learning disabilities, be screened for autism?

Dr. Jamie Capal: 44:16 Ideally, yes. In the general pediatric world, the American Academy of Pediatrics has set up a guidelines to screen their young patients for autism with the M-CHAT, which is just a questionnaire that you get at I think 18 months, 24 months, and then again somewhere between two and three, to screen for autism. We're getting better at that. Because one of the problems is that when young individuals are getting diagnosed with epilepsy, the other aspect of their development weren't really paid attention to as much. So, they're finding that those individuals who are getting diagnosed with autism much later because maybe they were spending more time really focused on the seizures. So, Yes. Those folks really should have good surveillance by their pediatrician, and if there are any concerns for development, or anything they should be referred on to developmental pediatrician for further work up.

Dr. Laura Lubbers: 45:21 So, this is really a place where parents could be advocating for that.

Dr. Jamie Capal: 45:24 Very much so.

Dr. Laura Lubbers: 45:26 Okay. Terrific. Another question. What evaluations are being done outside the brain, and EEG? Are people looking at the gut, the autonomic nervous system, sleep disruption, that are implicated in both epilepsy, and autism?

Dr. Jamie Capal: 45:46 Yes. There are definitely folks that are looking at the gut-brain connection. I think there's a lot of interest there. It's almost like these subtypes of autism, like EEG

is one, and then patients that have a lot of GI disturbances are another group. I think sleep can be disrupted for many reasons, and kind of overlaps with a lot of these groups. There's an autoimmune interest in individuals that potentially have an autoimmune component to their autism, which I again think is another sort of subtype that is worth studying. So, I think the more we learn about the underlying cause, then we're better able to study the clinical features because right now, we historically have been looking at autism as a set of symptoms. But if you study autism just as the symptoms, and you have hundreds of causes behind it, you're not really going to learn anything until you get at what is the cause. So, yeah there's lots of interest in these different areas.

Dr. Laura Lubbers: 46:56 Great point. There was a question about what type of preventative treatments would be given to a person with autism, and abnormal EEGs, but it sounds like we really need to understand the biology.

Dr. Jamie Capal: 47:07 Correct. We don't know. I know that people have been interested... There have been some small studies that have put kids with abnormal EEGs on Depakote for example. And really haven't found a lot of benefit for... The interest is do we put them on medicine to prevent epilepsy? Do we put them on medicine to improve their EEG? We don't know, because I think the reason why people are interested too is looking at benign rolandic epilepsy, for example. Those individuals may have a few seizures, but they have a lot of underlying EEG abnormalities when they're sleeping. Some groups found if you treat the EEG, it may improve their cognition. So, the same thought is in this group, but nobody's ever done a big enough study to tell us is that actually worth it? Does it do anything? So, that question is still very controversial, and nobody is really studying it right now. So, it definitely needs to be studied.

Dr. Laura Lubbers: 48:13 Another question that's come in, it could be very difficult to get a non-sedated EEG on many children with autism due to sensory, and other issues, especially an overnight.

Dr. Jamie Capal: 48:26 Yes.

Dr. Laura Lubbers: 48:26 Are there other ways to detect EEGs with a headband, different, nontraditional approaches to EEG measurements, and what their relative accuracy is? Are people trying different approaches?

Dr. Jamie Capal: 48:46 I know that in certain research world, that they're using the EEG cap. One group, what they've done is they actually desensitize the children by having them wear a hat, and so they got used to it. And so, then when you put the cap on, they're already kind of used to that feeling, and those EEGs are actually pretty accurate versus the traditional putting on the leads, and being a bully. Now, a lot of times in my situation, we don't do that clinically, I'm sure there's a lot of reasons financially, and training wise. But I know in research to really get all of these children to get EEGs they become really creative at desensitizing the kids. So, all of our studies, we do EEGs on all of our kids and are actually pretty successful. So these big technology companies have come up with very creative ways to get the information.

Dr. Laura Lubbers: 49:48 Terrific. That's great to know that the technology continues to try to improve, and keep up with this issue.

Dr. Jamie Capal: 49:55 Yes.

Dr. Laura Lubbers: 49:57 We've got one more question.

Dr. Jamie Capal: 49:58 Okay.

Dr. Laura Lubbers: 49:59 What's involved with genetic testing, and where can we direct people for more information?

Dr. Jamie Capal: 50:06 Yes. So, genetic testing can be done several ways. Typically, and historically it's been a blood test. Your neurologist, or developmental pediatrician can order it. Typically, what we do is a chromosomal microarray which looks at any deletions, or duplications in your genes, it's a good place to start. There are many companies that have developed these genetic panels, which can be done by blood or saliva. Each panel is different, and geared toward a certain set of genes that they're looking at, but there's an autism, and developmental disability panel for example, there's an epilepsy panel. So, those are targeted tests.

Dr. Jamie Capal:	50:48	Then you have the bigger whole exome sequencing which currently, the Simons Foundation has a big study going on throughout the country called the SPARK study, and that is collecting saliva from the patient, and both parents, and looking at their exomes to really understand the genetic underpinnings of autism. You can even go to the Simons Foundation, look up SPARK study, and you can get a kit sent to your house. That's a great way to get some genetic information that's free for the families, because often genetics is not covered by insurance. They're getting better at covering them for neurodevelopmental conditions, but still not great.
Dr. Laura Lubbers:	51:30	Okay. Well that's terrific advice, and certainly we can make that information available as well. So, with that I would like to thank you Dr. Capal, for sharing your expertise with us. I think this has been a great interactive presentation, and Q&A session. We'd also like to thank the BAND Foundation for sponsoring today's webinar, and our entire webinar series. And, I'd like to thank the audience today for participating, for forwarding such great questions. If you additional questions about this topic, or wish to learn more about any of CURE's research programs, please visit our website at cureepilepsy.org, and please also be sure to register for our next Leaders in Epilepsy Webinar series. Our webinar, which is on May 14th, it's at 2:00pm central time, and in that Webinar, Dr. Zach Grinspan will discuss the role of epilepsy learning healthcare systems, and their potential impact on the epilepsy community.
Dr. Laura Lubbers:	52:31	So, with that I want to thank you all, and please be safe. Be well.