

CURE Webinar Infantile Spasms (Transcript)

- Laura Lubbers: [00:05](#) Welcome everyone to today's webinar. My name is Laura Lubbers, and I am the chief scientific officer of Citizens United for Research in Epilepsy or CURE. And I want to thank each and every one of you for joining us today. Today, November actually, is epilepsy awareness month, and CURE is pleased to present the third in our series of five webinars that highlight some of the key research that's being done on epilepsy.
- Laura Lubbers: [00:33](#) Today's webinar will focus on infantile spasms and will be presented by Dr. Jeff Noebels. Next week on November 21st, Dr. Ramon Diaz-Arrastia from University of Pennsylvania will present on post traumatic epilepsy. And during the final week of epilepsy awareness month, on the 29th, Dr. Elizabeth Donner from the University of Toronto will present on sudden unexpected death in epilepsy or SUDEP. All of these webinars are at 2 PM Eastern time.
- Laura Lubbers: [01:04](#) For those of you who may not be familiar with CURE, our mission is to cure epilepsy, not just treat it. Our goal is to transform and save millions of lives who are affected by this devastating disorder. We identify and fund cutting edge research, challenging scientists worldwide to collaborate and innovate in pursuit of our goal.
- Laura Lubbers: [01:26](#) We are one of the largest private funders of epilepsy research in the world, funding over 200 research projects in 15 countries. CURE has been a pioneer in many areas of epilepsy research, including SUDEP, where we've invested over four million dollars into research. CURE is also supporting development of a new technology that may be able to help detect seizures and alert caregivers. We also realize that anyone is at risk for developing epilepsy, because it can be acquired over time, and as a result of brain injury. We've just launched a new project funded by a grant from the US Department of Defense that supports a team approach to understanding post traumatic epilepsy.
- Laura Lubbers: [02:11](#) CURE has also been working to accelerate the understanding of infantile spasms, or IS, which is a devastating form of childhood epilepsy. These spasms generally affect newborns before the age of one, but in some children they may occur up to age two. Infantile spasms impacts about 1200 infants per year, and if they are not diagnosed and controlled quickly, they can significantly impact a child's development and lead to lifelong disability. CURE has worked to raise awareness of infantile spasms, and also sought to understand the causes and potential treatments for these spasms.

- Laura Lubbers: [02:50](#) A number of years ago, we assembled a team of researchers to study IS, and Dr. Jeff Noebels from Baylor College of Medicine was one of the members of the team, and he has joined us today to tell us more about IS. Dr. Noebels is the [inaudible 00:03:04] endowed chair of neurogenetics, professor of neurology, neuroscience, and molecular genetics. He's the vice chair for research in the department of neurology. He's also a past president of the American Epilepsy Society and has received numerous awards for his pioneering research on epilepsy.
- Laura Lubbers: [03:25](#) Before Dr. Noebels begins, I'd like to encourage everyone to ask questions, be thinking about questions during the presentation, and go ahead and submit them during the presentation by typing them into the questions tab of the GoToWebinar control panel and clicking send. My colleague from CURE, Brandon Laughlin, will read them aloud during the Q and A portion of the webinar. We do want this webinar to be as interactive and as information as possible. However to respect everyone's privacy, we ask that you make your questions general and not specific to a loved one's epilepsy. I also want to mention that today's webinar as well as the entire leaders in epilepsy research webinar series will be recorded and available on the CURE website. So with that, I'd like to turn it over to Dr. Noebels.
- Jeff Noebels: [04:13](#) Well thank you so much Laura, and it is a pleasure to join you and everyone today talking about this important topic. But first before I begin, really a heartfelt thanks to the CURE foundation, for all of you who support it for all you do. The CURE has made an enormous difference in getting particularly young investigators started in basic science studies of this disorder. And everything has changed really since it began its program to improve the future of people with epilepsy. So we're all really grateful for this opportunity to work with you and educate all of us as to different types of epilepsy and what we're doing about it.
- Jeff Noebels: [05:03](#) So today I'll be speaking about infantile spasms, and I'd like to divide the talk into two major categories. First a clinical overview of what this form of epilepsy is. And then a little bit of an insight into the research project that we began thanks to the CURE funding into an area of seizures that we had no previous experience in because there was very little opportunity to study it in the basic laboratory. And our ability to move it forward thanks to the CURE project has got me really excited about it. However it is really one of the most challenging forms of epilepsy that we've studied so far. But let me tell you more about it.

Jeff Noebels: [05:55](#) So our laboratory actually when we think about epilepsy, we think about genes, and I'll tell you why. So the Blue Bird Circle Developmental Neurogenetics Laboratory was started about 30 years ago here in Houston, Texas by the Blue Bird Circle, a group of women who chose pediatric neurological disorders to support. They support a clinic in the Texas Children's Hospital and a laboratory, the one that I direct, that is focusing on tomorrow's child. What we can do and what we can learn to make a difference so that we don't keep treating patients the same way. And our approach is really kind of a simple one, if I can bring it up on the screen. Let me see here. There we go. Is really define the genes ... well it went by quickly. Find the genes, find the mechanisms, and cure the disorder. And so that's why our approach resonates so much with the goals of CURE, which is not just to treat the disorder, but to really find cures for it and make it go away. And we couldn't move forward without not only CURE's support but a lot of other supports who over the years have helped us figure out how genes alter the brain to cause a particular kind of epilepsy and what we can do to prevent it.

Jeff Noebels: [07:28](#) So infantile spasms. What is it? It's a severe childhood epilepsy disorder. It's also known as West syndrome. Reason was it was first described by Dr. West in a letter to the medical journal Lancet in 1841. So it's a very old described syndrome. And he described it from observing his own four month old son. And although not all three criteria for making this diagnosis were present at that time, there was no EEG in those days, he noticed the motor spasms that are so characteristic. And what they consist of is both arms that suddenly are outstretched, a very lightning movement, or it can be milder with the head bobbing forward if the child is sitting up, nodding, or entire flexion of the upper body downwards. These events only last a few seconds, they may repeat every 10 to 20 seconds, and we may even see clusters of them up to three times a day.

Jeff Noebels: [08:32](#) So it's a readily observable movement that interestingly resembles what is called a normal Moro reflex, which is seen in infants until the age of three to four months. That's normal. If you hold an infant, and mothers may have seen a pediatric neurologist perform this test, hold an infant lying on their back, in your arms, and you drop your arms to slightly, and the child will fling both arms out. And that's a normal response in a newborn. It will disappear until about three to four months. But then these motor spasms if they occur can happen starting about a month later or so, about six months is when they're first noticed. And it happens in about one out of 3000 infants every year.

- Jeff Noebels: [09:26](#) The second component of the diagnosis is hypsarrhythmia, and let me explain what that is. It's an EEG pattern that was discovered also a long time ago in 1952 by two prominent American electroencephalographers. And what you can see on the lower left of the screen is the normal pattern of an EEG, and you can see pretty clearly how abnormal this hypsarrhythmia pattern is. It's very high amplitude, large, slow waves, and it's continuous. It doesn't relate to the spasms itself. It's not seen in every case. It's in about two thirds or even 80% of the cases of children. Infants with infantile spasms also show this EEG criteria. But when you see the EEG, whether they have spasms or not, it's an important diagnostic for the infantile spasm syndrome.
- Jeff Noebels: [10:29](#) The motor spasms that I mentioned usually arise around three to 12 months of age. They can be subtle, and they're often, and this is a problem, unappreciated for some months. And the major goal is for early diagnosis. The outcomes will be better the sooner you detect this. The children are usually evaluated with the EEG and an MRI imaging and some other lab tests. And these spasms actually may disappear on their own or following treatment. We'll talk about the treatments available. But what they usually indicate is they're the harbinger, they are the early warning of more to come. And so it's not a positive sign. The next thing that can happen will be regular epilepsy type seizures, motor seizures, and then developmental delay of varying qualities and patterns, but intellectual disability, autism are very common, speech delay. And this is why we consider it so severe. It begins early and it has a history that seems to get worse.
- Jeff Noebels: [11:39](#) So there are a few therapies that are available for infantile spasms. The front line ones are ACTH, adrenocorticotropic hormone, vigabatrin, steroids. And these seizures in the epilepsy portion of the disorder may be highly resistant to other antiepileptic drugs. And overall there are no proven treatments for the cognitive deficits. There are treatments we'll talk about for the spasms and seizures.
- Jeff Noebels: [12:14](#) So a physician when they encounter this has a series of decisions to make, and I'm showing you the cover of a journal *Epilepsia* where they feature the decision tree of what needs to be done. The principal things are really in terms of predicting the future is for the patient is the imaging results. And if the MRI is judged to be normal, it's termed a cryptogenic disorder. And about half of those children have a positive outcome. But when lesions are found, and this is also a finding of brain malformations and other events that might happen during birth, hypoxic lesions, the outcome is considerably less positive it's down to about 6%. I mentioned ACTH, that can be given

early and yield a dramatic response in some cases. It was again used first a long time ago, in 1958. And it's still used today. The mechanism is unclear. It's a hormone, has many major effects on cells as they grow and develop in the brain. It also has some important side effects in terms of its suppression of the immune response. So it's not the best medicine to have, but it's the only one that is a front line drug.

Jeff Noebels: [13:50](#)

Vigabatrin is another more classical antiepileptic seizure drug. It works. It's part of the protocol. But it also has some side effects, some retinal damage, and it's not the best thing to give, but it's better than nothing, because it has been shown to work. But overall, just to give you the view that this is a complicated seizure disorder, there's an inadequate response to treatment. And there are some successes, but many failures too. And that's why it's been targeted by CURE for special attention and research.

Jeff Noebels: [14:33](#)

For those of you who want to learn more about what it's like to discover and live with a child with infantile spasms, this is one of several nice YouTube videos. This one was produced by the Child Neurology Foundation. They interviewed Liz and Jeff, were two parents who tell their story online. It doesn't last too long. But they show pictures of their son Nicholas. It shows the classical pattern of the spasms themselves. And they describe what they felt was a gratifying response to the early treatment they were fortunate enough to have. But we don't know what the ultimate outcome, I think there was some speech delays, some other non-seizure issues that still complicate these cases.

Jeff Noebels: [15:25](#)

So in summary, a complex disorder, multiple causes. So the first one that we know about is the genetic cause. So you can be born with the mutation in the gene. And one of them, important one, is tuberous sclerosis, which causes focal brain abnormalities, dysplasias they're called, malformations. And there are over 50 rare metabolic disorders that also related to this presentation of seizure disorder. You can acquire it apparently early maternal CNS infections in the womb, and perinatal hypoxia have been known to cause this. They don't always cause this, and so these might be happening to people that have some other risk and this just aggravates the situation. But it can be thought to be an acquired epilepsy as well. And where we stand now is that we've identified many genes, but we still know very little about their mechanism, why do they cause this particular form of epilepsy.

Jeff Noebels: [16:32](#)

I'm sorry, we should go back to that. We can't. Well the CURE strategy then is to recognize in all of epilepsy, all of our current treatments, only control the symptoms. Those of you who have experience with epilepsy knew we're managing the

presentation of the disease, not curing it. And there are no real established therapies that alter the course of the disease even before the first seizure.

Jeff Noebels: [17:01](#) But here's where we have an interesting advantage and why I've long studied genetic forms of epilepsy, because a single gene disorder can be diagnosed very early. Sometimes even before the first symptoms appear if there's a disorder that runs in the family. And that gives us an opportunity to actually get there before the damage is done. Now mouse models of single gene disorders offer valuable opportunity to explore these early interventions in developing brain to reduce the risk of epilepsy and its comorbidities before they even occur. And thanks to the genetic revolution, we're able to engineer mutations that are found in people and engineer them into the genome of a mouse and actually create a mouse that has the human disorder and use that mouse in the laboratory to study what the gene does to the brain and what we could do to prevent it.

Jeff Noebels: [18:00](#) So this is something that I want you to understand, that before epilepsy occurs there are things we can do, developmental windows for early intervention while the brain is still forming. So if you look on the left where a gene defect obviously is present from the moment of conception, and then a child is born at birth, and then you see this gradual appearance of neurological deficits, so many different forms, and one of them might be seizures and epilepsy. And it's at that point that typically we treat with an AED, and that's the way the management of many seizure disorders occurs. What we're talking about now is looking at the events of the brain before the appearance of epilepsy and see if we can identify a point and identify mechanisms of the brain that we might be able to gently retune and see if that would actually prevent the disease from showing.

Jeff Noebels: [19:03](#) And obviously if we know what the gene is, we can have enormous insight into what drugs we might use or what we might do, and certainly what we can learn about what's really causing this disease in the first place. And the more we learn, the more we might be able to go use unconventional drugs, like hormones, ACTH as an example of that. Other factors that alter the way cells grow and connect with each other and see if we can actually rebalance the network. It's sort of like modifying a computer using more software rather than hardware and see if we can change the way the instructions are being processed in the brain. And of course the more we learn, the more we may be able to do this earlier and earlier. So this is what's enormously exciting and why I'm optimistic about the new tools that we have available to cure epilepsy rather than just treat

them. So this applies not only infantile spasms but other forms as well.

Jeff Noebels: [20:09](#) So why did we choose Arx? We missed ... here's the next slide. So what I want to tell you now for the rest of this time is the project that CURE helped us get off the ground and continue to study. And it was published in a very nice journal, the Science Translational Medicine, and the title of the paper was Neonatal Estradiol Stimulation Prevents Epilepsy in the Arx Model of Infantile Spasms. What I'd like to tell you now is why Arx, what is Arx, why did we use estradiol, which is an estrogen, and can we translate this discovery? As you can see from the title, we prevented the epilepsy from occurring in this model. And can we do this in humans too?

Jeff Noebels: [21:01](#) So a little bit of information. Why did we choose the gene Arx? Well it turns out it was the very first one to be described as an encephalopathy gene in epilepsy. So that's a gene where not only seizures are produced, but learning deficits as well, and various other neurological problems. So we were very happy to begin with the very first one. And lo and behold, there was a paper showing that this, a mutation in this gene Arx, A-R-X, was associated with the cryptogenic form of West syndrome. That means infantile spasms with no obviously brain abnormalities found in the MRI. So we said let's engineer that mutation into a mouse. Let's make a mouse model of this disease and see what we can do.

Jeff Noebels: [21:52](#) So I'll tell you the second reason we chose Arx is that unlike many genes that are expressed in all cells in the brain, this gene was only expressed in a small subset known as interneurons. What are those? If you look in the picture, you'll see two brain cells, well a large one that's marked, and that's an excitatory neuron, that's signaling and giving a positive effect in the brain. These red, smaller red cells are known as interneurons. They are the brakes. They inhibit the larger cells from firing. So these interneurons are essentially the brakes of the nervous system. When you want to send signals out, you do, and then the inhibitory interneurons are there to stop the firing. That's an essential part. It's sort of like tuning your radio. You can get to a good signal, but if there's a lot of static and you fine tune, you will get rid of all the static and get a very clear signal. That's what these interneurons are there to do, to essentially fine tune, the networks in your brain allow them to do their function.

Jeff Noebels: [22:57](#) So it turns out that this gene Arx is only in these inhibitory cells. That makes life a lot simpler for those of us trying to fix whatever problem these interneurons have in this Arx mutation brain. And what we had learned from other various science

studies down here on the left, is that Arx is very important for the way these cells migrate while your brain is developing. When you remove Arx from the brain, these inhibitory interneurons, which are all clustered here, fail to migrate to their proper positions in the cortex. So they're not where they're needed, so they can't work properly at all. So and this is just a description of what happens during development. We know exactly where these cells are, where they end up, where they should be. And we know also that when you mutate this particular gene, they don't get to the right place.

Jeff Noebels: [23:53](#) So what can we do? We engineered this mouse, and it was really the first mouse model. You're about to see him have a spasm. This was the first time we had a genetic model. These are sleeping little pups. And he just had one. And you can see a major flexor spasm that you don't see in the other wild type pups when they sleep. Sleeping mice have little twitches, but they don't have those large flexor spasms. These mice grew up to have seizures. They also had cognitive impairments. They avoid social interactions, similar to what autism behaviors look like. And so they were turned out to be the first and very important single gene model of infantile spasms. So a perfect opportunity to see how we could prevent this from happening.

Jeff Noebels: [24:48](#) And we chose estrogen, which is one form of estradiol, which we're all aware of is present and has feminizing characteristics. It's also made in the brain of both men and women. So estrogen is a growth factor. It's a neurosteroid just like ACTH that is present normally in the brain. Estradiol it turns out from studies in songbirds, believe it or not, is where it was first shown to have what we call motogenic properties. It can make cells migrate, and in fact below, I won't describe it, but is a paper that I saw, and saw that estrogen would promote migration and recall that the Arx mutation prevented normal migration cells. So I thought why don't we just add some estrogen to this developing brain and see if we could push those cells along and encourage them to migrate to their proper position? That's what it does in birds as they develop their song, which is a form of communication. So we reasoned this might actually be an important potential therapy.

Jeff Noebels: [26:07](#) And of course it was already known that estrogens are very good for the developing brain in a number of other ways. They reduce inflammation, they protect cells from dying, and they help repair injured cells. So we thought gee, all of the signs point toward an interesting opportunity to help this brain develop a little more aggressively despite its problem.

Jeff Noebels: [26:34](#) So what we did was take these mutant pups and wild type pups, and we looked at the first week after birth and gave them

estradiol every day for a week. A very tiny amount, 100 times less than what would cause a feminizing effect. And we treated them, and what you can see is that in the group that was treated, none of 16 of the mice were observed to have spasms on the day we tested them on P10. We observed them for a prolonged period of time. There were no spasms in the treated group. Five of the 16 mice that were untreated had spasms that day. So we really made a significant difference.

Jeff Noebels: [27:21](#) It also reduces seizures. When we took these mice and treated them every day for the first week with estradiol and then waited a month or even two to follow their EEGs, we found that the seizures that would normally be present were not present at all. And if you look over here, out of eight mice, only one that was treated had one seizure during a 12 hour period that we monitored. Whereas six of them had between two and three seizures on that similar day if they hadn't received it. So we made a dramatic difference in the number of seizures they developed several months later.

Jeff Noebels: [28:02](#) Finally, and I won't ask you to stare at this for very long, but we were able to show that the estradiol treatment caused these interneurons to return to their normal positions as a group. And so we had restored physically some of the wiring mistakes that were present without this estradiol treatment.

Jeff Noebels: [28:29](#) So that's just a short version of what could be a very long talk, but I want to leave you with the impression that we can do something early on in these genetic disorders so that we found that early estradiol stimulation modifies the disease trajectory. These mice are certainly far better off than they would have been without the treatment. And we're now looking toward the future with our next steps. So will this work? It worked for one gene. Would it work in mouse models of other genes that cause infantile spasms? Is it more of a universal treatment or is it very specific only for people with this particular problem? We need to understand that in order to move it forward. Also to translate it into human, we have to make sure that estradiol, even though it's naturally occurring in the brain and is good for you, is it really safe to stimulate the brain at that particular point early on and will these children grow up to be as normal as they could be? And so those kinds of studies actually are coming in from around the world, and so far the results are extremely good. It seems to be that adding a little bit of estrogen is perfectly safe.

Jeff Noebels: [29:45](#) You should know that when an infant is still in the womb, the maternal estrogen levels that it is exposed to are a hundred times larger than what happens on the day of birth, when the child is on its own and all of a sudden the maternal blood estrogen is not present anymore and they're on their own to

make their own estrogen levels. So the brain is already used to being exposed to very high levels of estrogen anyway.

- Jeff Noebels: [30:13](#) The last point is can we learn to diagnose and spasms in time to protect the developing brain? We still do not know whether we can get to human brains early enough. We started on the day of birth because we knew these mice would develop their genetic syndrome. We don't know that in the case of humans. We have to wait until they show signs of the first problem before we can get going. So we need to learn a little bit more about how long a time window we have to do this. But this I think gives you a good idea of the power of the approach and the many opportunities that I think we're going to have to learn a lot more about this disorder and new novel treatments.
- Jeff Noebels: [31:02](#) So I'd like to end just by thanking the incredible scientists who helped with the story. First with Maureen Price and Fang Deng who generated the first mouse model, Pedro Olivetti was an MD PhD student in our laboratory and performed the estradiol treatment and showed how effectively it works. And Meagan Siehr is now currently funded by CURE to do her PhD research which centers on the mechanism of how does the estrogen really work? Estrogen has a number of different ways it can support cells and change their function, and we need to learn a lot more about that, and that's what her doctoral dissertation will be on. So let me just end here by thanking CURE again for their generous support of our research. I'm happy to take questions.
- Laura Lubbers: [31:54](#) Thank you so much Dr. Noebels. We really appreciate that great overview of your work in how scientists approach these types of really difficult questions. So now we'll begin the question and answer period. Again, if you have any questions, please submit them in the questions tab of the GoToWebinar control panel and click send and Brandon will then read them aloud. Brandon, are there any questions that have already come in?
- Brandon Laughlin: [32:20](#) Yes there are. I will go ahead and start with the first question for Dr. Noebels. Dr. Noebels, do all IS cases have a genetic cause? And if they don't, what are some of the other presumed causes?
- Jeff Noebels: [32:38](#) Right. So, IS, it's not incredibly rare, but it's uncommon. And among those who have it, we have now discovered that there are certain genes that are now well known that can underlie the syndrome. I mentioned tuberous sclerosis and Arx. There are some others. I won't give you their names. But there are probably five to ten genes that we know about and we can look for in the case. And that can likely explain features of the syndrome that the infant has. As far as acquired causes, I

mentioned perinatal insults and maternal CNS infections have been associated with it. Beyond that, that seems like a general category. We don't know specifically which viruses, what kind of insults, because they often created a lot of damage in the developing brain, and so we can't always predict what kind of epilepsy will emerge from that. So there are both genetic and acquired causes of this syndrome.

Brandon Laughlin: [34:03](#)

Great, thank you. The next question actually is related to the previous one. I understand that IS results secondary to a brain injury. Does the research differentiate between genetic causes of IS and those secondary to a brain injury?

Jeff Noebels: [34:22](#)

Well, again, what we know from these and the research is usually the firmest information we can get is from animal models at a very basic level. So we don't have too many of those models in the animal. There are various drugs that can be injected into a developing brain that seem to produce spasms and even the EEG counterpart, the abnormality, the hypersarrhythmia to study. But we're not confident always that those are the same as what happens in human. It's just a model. They allow us to study basic parameters of this disorder without really telling us this is what any child might have. So there are ways of approaching this scientifically. The genes are probably the clearest and most reproducible way of learning more about each child with infantile spasms.

Brandon Laughlin: [35:31](#)

Great. The next question is actually a two part question as well. Do infantile spasms have an autoimmune etiology? And have auto antibody prevalence been studied in this population?

Jeff Noebels: [35:44](#)

Well that's a wonderful question. So in the group that CURE brought together, we're a group of scientists and clinicians, and we sat down and quickly realized that there are many questions we don't understand. The autoimmune concept, just to explain to people, is that the nervous system in the body will start to generate antibodies against itself. Obviously a very dangerous chain of events, because you begin to attack normal structures in your brain. And there are several forms of childhood epilepsies in particular that have this autoimmune cause, where if you look at the cerebrospinal fluid, you can find antibodies directed against the very molecules that you need to properly signal the brain. These receptors can become degraded by your immune system and seizures can result. I'm not certain that we have a clear knowledge base on whether this is one form, whether infantile spasms can arise from it, but it's a very tempting hypothesis that deserves to be explored. The forms that I'm aware of don't cause infantile spasms, but they do cause seizures.

- Jeff Noebels: [37:18](#) Now on the other side of ... question, is that well why does prednisone and ACTH these steroids, why are they so effective as treatments? Because we know that they do impair, they tune down the inflammatory response in your body. That's why they're usually prescribed. So therefore, does that mean that the infantile spasms was an inflammatory disorder? Not necessarily, because these steroids have many other effects, including actually acting on GABA receptors which is the target for many of our best antiepileptic drugs. So there is some evidence that perhaps there could be an inflammatory response. I don't believe it's ever been well studied or firmly demonstrated. But just because a prednisone works so well when it does in blocking infantile spasms, doesn't mean that that's the mechanism for generating.
- Brandon Laughlin: [38:29](#) And you actually kind of touched base on the next question, which was a follow-up question to that. And how often are anti-inflammatory drugs used in this population?
- Jeff Noebels: [38:42](#) Well in the sense of that prednisone is the front line treatment for these infants, so I would suspect that whenever it's properly diagnosed and the prednisone is available, that is the first medicine that the child will see. It doesn't always work. Also as I mentioned, infantile spasms sometimes can go away anyway without treatment. Another interesting aspect of the infantile spasms part of this syndrome, it's what brings the child to the doctor's attention. It is not necessarily itself a epileptic seizure in the sense that it may not actually be damaging the brain. So as I mentioned, one of the fascinating features of this is that it looks like a normal reflex. It's just present in the nervous system at an age when that normal reflex would have disappeared. There's no sign in the EEG, in the rest of the brain, of a seizure when this happens.
- Jeff Noebels: [39:54](#) And so to my mind, we don't have to worry as much as we do with convulsive seizures about whether the event itself is actually damaging to the brain. We would like it to go away, wish it wasn't there in the first place, but it's really just a tell tale that something developmentally is wrong in the wiring of the brain that these reflexes persist in some way or return. And as nice as it is to get rid of them, the infantile spasms themselves to me aren't as much of a danger as just an important warning sign that there's something else the matter, and if we know how to treat seizures that are to come, maybe we can prevent them.
- Brandon Laughlin: [40:49](#) Great, thank you. Next question is actually along the lines of your former research, and do you know whether combination treatment with estradiol and ACTH or vigabatrin will provide a greater level of effect?

- Jeff Noebels: [41:07](#) Oh that's a wonderful question. In fact, some of those studies are ongoing. So one of the things we decided among the CURE group would be to find out if in our model does our mouse model respond to prednisone, and we found out that it does. But what we haven't done yet is to combine the two, prednisone plus estradiol, and see if that would really allow us to either use smaller doses or treat for a shorter period of time. Those are studies that we would really like to complete and get an answer for.
- Brandon Laughlin: [41:47](#) Great. Next question. Do you think that there would be a difference in the actions in males compared with females in your study?
- Jeff Noebels: [41:56](#) Well that's interesting, because this was an excellent gene. And for everyone, that means that males will only have a single X chromosome. If they have the mutation on that chromosome that they inherited, they will have the disease. Whereas a female has only 50% chance and possibly no chance because she has a second normal X chromosome that could protect her from the disorder. Whereas the male has only one X chromosome to rely on, and if it has the mutation, you're affected. So all of our studies are actually, and for this particular gene, are done in males, because they're the only ones that are affected. Now other genes may not show that sex difference and they'll be very interesting to see if estrogen levels, which might be different in females, are actually protective in that sense. So we don't know the answer to that question, but it's interesting.
- Brandon Laughlin: [42:58](#) Great, thank you. Next question. You mentioned TS among the etiologies of IS, and a significant proportion of patients with the TSC mutation develop IS. Do we know what proportion of patients with IS have a TSC mutation? And on these lines, could you share your thoughts on the potential of mTOR inhibitors for the treatment of IS?
- Jeff Noebels: [43:25](#) Those are good questions, but I'm sorry, I don't know the answer. This is still really rare, and I'm sure there's some studies that could answer that, your first question. But I don't have that fact at my fingertips. But we're talking about an uncommon ... both disorders are somewhat uncommon. You hear about them a lot because we have the genes and we're working on them intensively. But I don't have the epidemiology of that question yet. But the mTOR inhibition issue is certainly an interesting one, and just like the estradiol, mTOR inhibition seems to be remarkably effective in certain kinds of epilepsy, including TS. But I don't know whether it'll be effective in all forms, or even same forms as the ones where estradiol will work. So again, these are open questions, and see how well we can prevent

damage using these different sort of targeted therapies for very specific molecular pathways and cells.

Brandon Laughlin: [44:44](#) Great, thank you. Next question is asking your opinion on the existence of truly idiopathic infantile spasms where they were normal prior to diagnosis, rapid response to treatment, and normal tests, and normal developmental outcome.

Jeff Noebels: [45:01](#) And I'm sorry, the first part of that question was?

Brandon Laughlin: [45:04](#) Just was actually regarding your opinion on the existence of truly idiopathic infantile spasms.

Jeff Noebels: [45:16](#) Well my opinion, that word idiopathic helps a lot of people out because it's a Greek term. That means we have no idea of what's going on. So idiopathic infantile spasms up until recently was all of them were idiopathic. Now we have a few genes for some of them. But I can't really comment as a group on what the natural history of idiopathic infantile spasms are. If you go into the old literature of infantile spasms before we knew these subtypes, then everything you read would be true, because they couldn't distinguish between different types. Now you wonder whether something is idiopathic because you haven't looked for all the things that we do know about yet. So you begin to question the use of the term idiopathic because we know there are certain answers. And in fact, the field of epilepsy as a whole has seemed to move away from the term idiopathic epilepsy, and now they call it genetic epilepsy under what I guess is the optimistic assumption that everything that doesn't have an observable cause during the lifetime must be genetic, and therefore has a discoverable genetic problem.

Jeff Noebels: [46:38](#) We won't probably ever be able to discover every single gene that contributes to epilepsy in every single person. But there is a sense that the entire field is now assuming that most cases, the more we study them, if we can get a pure culture of a specific type of epilepsy and study it intensely, we will find the cause of that particular type. But I think all of our listeners know that epilepsy comes in so many varieties. Different ages of onset, different seizure types, different responses to antiepileptic therapy, that we know we're dealing with a very complicated disorder. Certainly it's as complicated as all the cancers you've heard about, and that we just need to learn a lot more about these disorders before ... and we need to split them apart and look at them, and then see if we can lump them back together.

Brandon Laughlin: [47:40](#) Great. Thank you. Do you know of chloride regulation deficits in interneurons that impair migration or development of interneurons to cause infantile spasms?

- Jeff Noebels: [47:53](#) That's a very interesting question. Not off the top of my head. Most ion channel mutations, chloride channel is one of them, are not known to interfere terribly with migration. At the moment, there's a migration disorder in one of a number of forms is probably the best explanation for infantile spasms as far as I know. So of the chloride channels, I can't think of one. There's one in mice that obliterates the hippocampus, and that's not anything like what you see in infantile spasms. But the other ones that are either triggered by electricity or opened by GABA inhibitory transmitter, I don't know that there are ... there should be defects in migration. I don't know of a specific model where that's been shown, and it shows to have the infantile spasms phenotype, but I would not be surprised if there's one about to be reported.
- Brandon Laughlin: [49:07](#) Great, thank you. The next question actually is regarding CURE's, the team science approach to the IS initiative. And the question is can you explain what this means and do you think that this approach may lead to discoveries that could lead to breakthroughs sooner?
- Jeff Noebels: [49:28](#) Thank you for that question. Yes, absolutely. And this is something that I think is happening all over science, but really needs to happen fast in disease or oriented sciences because we're all counting on these breakthroughs to come. And what's happening in science right now is the enormous growth of very powerful tools, both ways of manipulating brain cells at the molecular level and of tracking their functions with amazing tools of micro imaging and electrophysiology of single cells and of large groups and networks of cells. We're really starting to be able to powerfully examine the nervous system, when it works and when it doesn't work properly. So all of those techniques require time and skill, and no one laboratory really can do it. The ones that really have a tool that they can perform correctly don't know as much about disease, and the people with a lot of disease background don't necessarily have all the tools. So the idea of getting together with a focus group and attacking a problem, such as was done with the CURE initiative, was really a smart thing to do, and I think we need to see a lot more of it in the future.
- Brandon Laughlin: [50:59](#) Great. Next question. Has the ketogenic diet been used as a first line approach to treatment for these babies?
- Jeff Noebels: [51:12](#) Well, I'm not a pediatric neurologist, I'm an adult neurologist studying the developing brain. So I don't have firsthand information. The ketogenic diet keeps coming up in every form of epilepsy where the conventional drugs don't work well is not the front line treatment for infantile spasms, but it is certainly something to try if the front line treatments haven't given the

desired effects. It's a difficult treatment. I think it's been tried in most different forms of epilepsy. I don't know that anyone is claiming that it is the second line, but it's certainly available and could work in some cases.

Brandon Laughlin: [51:55](#)

Great. Thank you. It looks like we are coming to the five minute mark of our presentation, so I'll go ahead and turn it back over to Laura Lubbers to conclude the webinar.

Laura Lubbers: [52:09](#)

Thank you so much Dr. Noebels and Brandon for that wonderful Q and A question. What terrific session, what terrific questions that came out of this. So I'd like to thank all of you for submitting those questions and for participating in this webinar today, and to give Dr. Noebels a special thank you for sharing your wonderful knowledge of childhood epilepsy and specifically around infantile spasms and how you approach studying these very challenging disorders. Everyone can learn more about infantile spasms at our CURE website, which is www.cureepilepsy.org, or you are welcome to email us at info@cureepilepsy.org. Again, I-N-F-O @cureepilepsy.org. You can find out more information on CURE events during epilepsy awareness month, including the my shot at epilepsy campaign on the website. And please be sure to register for our next webinar on November 21st at 2 PM, when we will be discussing post traumatic epilepsy. I hope everybody has a wonderful rest of your day. Thank you again for joining us.