

Seizing Life, episode 130
Infantile Spasms: The Facts, The Research, and The Hope for the Future
Guest: Dr. Chris Dulla
(Transcript)

Kelly Cervantes: Hi, I'm Kelly Cervantes, and this is Seizing Life, a bi-weekly podcast produced by Cure Epilepsy.

Today I'm happy to welcome Dr. Chris Dulla to the podcast. Dr. Dulla is a professor and vice chair of neuroscience at Tufts University, where he also runs a lab which conducts several ongoing epilepsy research projects. He has also been the recipient of a Cure Epilepsy Taking Flight award for research into infantile spasms. In recognition of Infantile Spasms Awareness Week, which is December 1st through December 7th, Dr. Dulla is here today to talk about infantile spasms, his laboratory's research and how its findings may lead to improvements in detection and therapies. Chris, thank you so much for joining us today. To start things off, why don't you give us a little background in how you got involved in epilepsy research?

Chris Dulla: Sure. Well, thanks for having me. It's a pleasure to talk with you. I love talking about epilepsy research so I'm glad to be here. I started my journey into epilepsy research way back in graduate school, about 20 years ago now, being really just interested in how the brain works. I'm kind of like a science nerd, and I love to try to understand how synapses function and how drugs help your brain function properly, and so from that, I kind of got interested in how the brain functions in epilepsy. In addition to being a debilitating disorder is, from a scientific point of view, a fascinating disease because it really shows you what happens when the brain isn't working properly. And not all neurological diseases are like that. So you get things like auras and you get kind of odd behaviors of the brain and experiences associated with them, and it really just intrigued me.

So that kind of drew me into the area. Along with epilepsy, research is a great area for mentorship, so I got a lot of good mentors and people who taught me about epilepsy research and models of epilepsy. And then finally, the thing that sealed the deal to keep me really interested in epilepsy research is, once I started working on that, I met so many people who were affected by epilepsy. I really had no idea prior to that how common epilepsy was, but as soon as... Someone would ask me about what I work on, I would say epilepsy. It was kind of shocking how often someone would say, "Oh, my sister had epilepsy," "My dad had epilepsy," And so I really saw firsthand how common it was and how much need there was to have new treatments and new understandings of epilepsy.

Kelly Cervantes: Well, it's amazing to hear on multiple accounts that people feel comfortable sharing with you about their epilepsy, but beyond that, that there's great mentorship within the field. I love to hear that. Now, one of your major focuses of research is infantile spasms, which is certainly near and dear to my heart, but before we talk about your research, I wonder if you can give us just a little

primer on infantile spasms or IS just for those people who are listening that may not be familiar with it.

Chris Dulla:

Sure, I'd be happy to. And I'll preface this by saying I'm not a clinician, I'm a scientist, so take everything I say with a grain of salt. But what I can share with you is what I do know. So infantile spasms is an early life epilepsy. It often begins in the first months or years of life, and parents and families will kind of experience that everything seems like it's going normal with their child, they're developing as they should, and then they might start to notice that their child will start to have these spasm-like behaviors. And often, they seem normal. They don't seem like something that would really be super concerning at first. And so that's a key thing about infantile spasms, is that early diagnosis is key. So when you see these kind of spasm-like behaviors, that's something that you should take seriously. So kids will do kind of what they call a flexion extension spasm where their arms go up and their body gets stiff and it'll only last a second and then it'll go away.

And during that time, what we think is happening is the brain is going into an inappropriate epileptic state, something that's damaging the brain. Then over time, that type of epileptic activity will kind of evolve. And as kids get older, they'll switch from this spasm-like behavior into what we normally think of as a seizure behavior where they'll have convulsions or maybe they'll fall or lose consciousness. And so there's this common progression of early life spasms into seizures as kids get older. So early onset, couple different types of seizures that occur. And then the other thing that's important to note is lots of different things can cause infantile spasms. It can be caused by genetic changes, genetic mutations, it can be caused by difficult births where a child might have a hypoxic or ischemic event, infection. Lots of other things can kind of lead to infantile spasms, which makes it difficult to treat and kind of sometimes difficult to diagnose. But that's a quick snapshot of the basics of infantile spasms.

Kelly Cervantes:

Yeah, I think you brought up a good point there that infantile spasms isn't a diagnosis, but a symptom of some other issue, which is the case for all epilepsies. But it is, it's really tricky to detect in the beginning, especially... I talked to so many parents, they're like, "I'd never heard of infantile spasms before." And it doesn't always present the same. We see this sort of... If you look it up online, you see the arms stiffening, but it can also be a head drop. In my daughter, we would see her eyes flutter. It was something so insignificant, and I think a lot of parents can have questions about that. Where should they turn to for a diagnosis if they're not sure and they're nervous?

Chris Dulla:

Yeah. Well, that's such a good question, and as a scientist, I can share with you that I had the same thing trying to learn about what infantile spasms was when I first started to become interested in it, pinpointing what it is, what causes it. Even for someone who's focusing their studies on this, it's hard to understand, so I can definitely get why it's really challenging for parents to try to do that in their day-to-day life when they're not thinking about these kinds of things. So to answer your question, I would say my experience with people whose kids are

going through this is never doubt yourself. If you think something is not quite right, then don't take no for an answer from your pediatrician. So I think the first thing is that pediatricians often are equally unprepared to help diagnose infantile spasms. They might say, "Oh, it's just like a muscle thing," Or, "I don't see it when you come into the office, so I don't know what to make of it." If your kid is going through this stuff, don't stop there. Don't take your pediatrician's word for it.

At the end of the day, the people that are going to be able to help you with this kind of thing are epileptologists. So those are neurologists that have a training in epilepsy and understanding epilepsy. And often, those people can be hard to access, so I can understand why there's a challenge to getting a good diagnosis, but that's who's going to be able to give you the most clear diagnosis and the most clear... As you mentioned, infantile spasms is a symptom, so someone like that is going to be able to give you the most clear sub-diagnosis, like, what is the cause? What's the genetic link that's driving this? And one thing that people try to do in this space is educate pediatricians.

So give information, give trainings, give pamphlets, things that you can put in the doctor's office so that a pediatrician who's having to diagnose everything under the sun, when they see a kid that has a spasm or when their parents are reporting that the kid's had a spasm, that they take it seriously and they understand what it is because it's challenging to diagnose, and as you mentioned, there's so many different things that can be the physical manifestation, so it can be complicated.

Kelly Cervantes: Yeah, absolutely. I usually tell parents, absolutely talk to the pediatrician, take a video of it if you can. You can have a three month wait or longer to get in to see a neurologist, let alone an epileptologist, so I usually recommend just go to the ER, ask for an EEG. It's better to know than to worry, and like you said, it's so important that we catch it early. How is it diagnosed? We talk about ask for the EEG, what do the epileptologists detect on that EEG that tells them it's infantile spasms?

Chris Dulla: Yeah, great question and complicated question to answer. So there's really two telltale signs of infantile spasms from the EEG. One is called hypsarrhythmia, and what that big scientific term means is, is chaotic EEG. So in the normal brain, parts of your brain are talking to each other, they synchronize with each other, the, when you open your eyes, when you close your eyes, when you go to sleep, the sort of state of your brain kind of changes and it changes together across the brain, it's kind of organized. So hypsarrhythmia is the exact opposite. It's a completely disorganized, chaotic brain state where one part of your brain is doing something, another part is doing something totally different and they're not talking to each other. And that has a unique, what we call, EEG signature. It will look a certain way on the EEG. So that's the first sign that people look for.

The second is what's called an electro-decrement, which, again, kind of big fancy EEG word, but what it sort of means is, in the normal brain, you have an

ongoing amount of electrical activity that's just there all the time, and it might switch or change, but there's always something. An electro-decrement means that that signal disappears, meaning that the brain kind of shuts off from an electrical standpoint for a short time. So neither of those two things, hypsarrhythmia or electro-decrement, really happen in a normal brain or a healthy brain. So if you see those things on the EEG, that's a sign that infantile spasms is probably happening. And for the first part, hypsarrhythmia, there's a lot of work being done to identify that as early as possible. So people are trying to characterize and identify things like, they would call, pre-hypsarrhythmia, where it's a signal that kind of looks like hypsarrhythmia, but maybe it's not meeting all the qualifications to be called hypsarrhythmia, like it's not long enough or big enough, but it has components that are a signature that that will evolve into later hypsarrhythmia.

So that's a place where, as we already talked about, early diagnosis is key. And so people are trying to figure out if there's ways you can detect hypsarrhythmia even earlier.

Kelly Cervantes: And you sort of spoke about this briefly before, but why is it that that early diagnosis is so important?

Chris Dulla: Yeah, good question. I think there's two reasons. One is, there's this idea that... It's a term called seizures beget seizures. So if you have a seizure, it's a pathological event, a bad event, that causes damage to the brain. And so the more damage that you have from more and more seizures, then the more the brain becomes wired to generate seizures. So if you come in and intervene early, then you're preventing all that damage that happens from the seizures happening over and over again. So that's kind of the first part of it. You want to stop seizures before they happen and you want to keep them from progressing. But I think for infantile spasms, the more important reason is that there are therapies that can be efficacious in some kids, and the earlier you start them, the more likely they are to work. So if you could identify pre-hypsarrhythmia in a time in which the brain is kind of entering this epileptic state and you could interrupt that process, then you have a better chance of the drug working and having a better outcome for that kid. So those are the two reasons.

Brandon: Hi, this is Brandon from Cure Epilepsy. Since 1998, Cure Epilepsy has raised over \$90 million to fund more than 280 epilepsy research grants in 17 countries. Learn what you can do to support epilepsy research by going to cureepilepsy.org. Now back to Seizing Life.

Kelly Cervantes: Now, I want to turn to your research, which is just so exciting, and the community is just so grateful for the incredible work that you are doing. Tell us a little bit about your lab at Tufts and the different areas of research that you're focusing on.

Chris Dulla: Yeah, I'd be happy to. Thanks for asking. So my lab obviously focuses on epilepsy research, and over the years, we've studied lots of different components of that

big epilepsy research kind of landscape. As I mentioned at the beginning, kind of how I got into this, I'm really just interested in a lot of our work about how does the brain function, how do brain cells talk to each other? How do things called glial cells support neurons in the brain? How is energy used by the brain? They're very basic questions, but they all have important implications for epilepsy research. So that's the first intro about just mechanistic basic science, is a lot of what we do. Obviously we study epilepsy. So we've studied infantile spasms using different genetic models of epilepsy, and that was a great collaboration with Cure Epilepsy and lots of different people that were part of the Infantile Spasms initiative, including people here at Tufts.

My collaborator, Michelle Jacob, is someone who I definitely want to give a shout out to on that. That was a project all about how brain development can be disrupted through different genetic manipulations and how that leads to long-term changes and how the brain is put together. We've also studied post-traumatic epilepsy. So another thing that can cause epilepsy is a brain injury. So sports injuries, people who serve for the military, veterans that get exposed to blast injuries. They're at very high risk for developing epilepsy later so we're very interested in studying that. We've also recently started to work on studying brain infections which are a big cause of epilepsy worldwide. And all of it gets couched in this sort of lens of how do cells talk to each other, how does that get disrupted and how does that lead to epilepsy? The last thing I'll add is right now there's definitely a really big interest in the field, and we're kind of part of this new direction in understanding how inflammation in the brain can cause epilepsy.

So obviously your body has an immune system and we've all experienced inflammation from an injury or a bug bite or something, but your brain has a totally different way that it responds to senses and responds to insult, and I think there's a lot of growing evidence that epilepsy is caused or exacerbated, made worse, by how those systems function in your brain. So that's a hot topic. And the last thing I'll mention, we work on a lot of different stuff. As I make this list, I'm seeing how many different projects we have going on. We're also really interested in brain metabolism. So your brain uses a ton of energy compared to the rest of your body. And if you're someone who has epilepsy or your loved one has epilepsy, you might've heard of what's called the ketogenic diet, which is a certain diet that is very high in fat, low in sugars, and for literally thousands of years, it's been used to help prevent epilepsy.

And so we study that. We study how does the brain use energy, how does it change how it uses energy in different metabolic states, and can we leverage that to prevent seizures, prevent brain injury, prevent brain inflammation, and things like that? Lots of different things, but [inaudible 00:16:08] as epilepsy is our central focus.

Kelly Cervantes: Absolutely. I think you covered on just about every fascinating and interesting avenue of epilepsy research that is currently occurring that is truly promising. And now I know that this can be a difficult topic, but I do want to touch on it

because I think it sort of helps explain why epilepsy research can be so slow moving and why it is so difficult, and that is the subject of animal models and trying to do this testing, which is necessary in order to get any sort of FDA approval way down the line from the work that you're doing. But can you talk to us in lay terms about creating animal models and why they're so important and how you have been a part of that process specifically with infantile spasms?

Chris Dulla:

Sure. Yeah, that's a great question. So the reason we work with animal models is because you can control every aspect of what happens in the animal's life when it lives in your lab. So you can control its genetic makeup, you can control the experiences it has, you can control the substances it's exposed to. And obviously in the real world when you're talking about people and kids, that's the exact opposite of how it works. So using animal models lets us try to isolate specific things that we want to study. And in the case of this infantile spasms project that we were involved with, we had an idea that a very specific protein called beta-catenin was really involved in infantile spasms. And that was based on genetic data from humans and our own experience with working with manipulating beta-catenin. But to really answer that question, we had to have an animal model because you can't go manipulate the brain of people, you can only kind of study what happens after the fact.

So in animals, we can go in and we say, okay, we think this protein is disrupted. We can disrupt it and ask if the animals go on to have a behavior that's like infantile spasms and if they go on to have seizures. So you can ask those mechanistic questions that let you take something you might've gleaned from clinical studies and really address it in a much more black and white way so you can really answer a question. And the other obvious thing that people will say about animal models is that you can test drugs in them. You can screen drugs that might have side effects that you wouldn't want to expose a person to, you can test drugs that may or may not succeed. By the time you get a drug in a clinical trial to a person, it's gone through so much testing of its safety, its efficacy, its engagement of what they call target, the molecule or pathway that you're interested in, that you're just trying to set yourself up for success as much as you can.

It takes all the groundwork and the years of those basic studies in animals to be able to get us to that point. And for the infantile spasms project, what was really fascinating, and I think it speaks to how informative animal models can be, was that these mice do almost the same exact thing as kids that have infantile spasms. Their behaviors are very similar. Their arms go up and their legs stick out, and they have these spasms that occur early in development that then switch to seizures later in life. Mice in general can't generate hypsarrhythmia. It's like their brains are too small to generate that big chaotic signal. But I mean, it's striking that you can have almost the same series of events play out kind of underscoring how useful animal models can be and how, this is kind of scary to think about too, but how similar we are to mice in some ways, at least, how our brains function.

Kelly Cervantes: That is alarming and also fascinating. In January of 2023, your lab's recent research into IS was published in the Journal of Neuroscience, and I'm going to read this quote, "Research suggests that an overabundance of inter neuron death seems to occur at the same time as the spasms associated with IS develop." Can you explain this to me? Because it sounds very exciting, but it's all in science researcher speak. In lay terms, what does that mean?

Chris Dulla: Yeah, yeah. Okay. So let's start by a little quick lesson on how the brain gets put together during development. And this is new stuff, this is not something you learned in bio back in high school or college, this is stuff that we're figuring out currently. When your brain is being built, one kind of theme that it uses is it makes more cells than it needs, and then as it figures out which ones it wants to keep, it kills off cells to end up with the right number of cells. That's perfectly normal. That's how your brain gets put together. So as I mentioned, there's two types of neurons in the brain. Kind of think about it in a simple way of excitatory cells, and you have inhibitory cells. So excitatory cells are born first. They're what mostly builds the brain's architecture. And then later, the inhibitory cells come in and kind of connect up with everybody and tune all the brain circuits and make the activity kind of what it needs to be.

And in that early brain development, and in mice, this occurs in the first few weeks of life, in people, this occurs in the final trimester of pregnancy, all of those inhibitory cells, they start to die off, as I mentioned. And the thing that we identified in our study was that they die too soon in an animal model with infantile spasms. So if you look later in life, the number of neurons is the same in our control animals and then in our model of infantile spasms. So it's a little bit tricky to discover or see, and that's why maybe it's been kind of challenging to identify some of the mechanisms. So you have to look really in that right window in development and you see that these inter neurons that are sculpting activity are dying too soon. And we think that has to do with long-term changes in how the brain is put together leading to later epilepsy.

And you mentioned that this overlaps temporarily with when spasms occur. So one question we're interested in figuring out is, are spasms occurring because these inter neurons are dying too soon and it's creating a window which the brain is hyperactive, and then you have spasms? Or are both the spasms and the inter neurons dying created by some other signal, like some other type of brain activity that's disrupted and that's damaging the inter neurons and killing them too soon and driving the spasms? So we're trying to kind of parse those things apart from each other, but the basic idea is that this normal loss of cells that happens during development is happening too soon in this model of infantile spasms.

Kelly Cervantes: That's an incredible discovery. And then what do you do with that? How does that potentially translate into a new treatment or preventative treatment or something?

Chris Dulla: Yeah, yeah. That's the challenge. You hit it right on the head. So in the lab, we can do lots of stuff that we can't do in people. So for example, we do a lot of what you might file under gene therapy. So we can introduce new genes into the brain with viruses, which is beginning to happen in people, believe it or not, but in our context, we can introduce viruses that will make those interneurons more or less active. And so we ask, if we can keep the cell active or if we keep it from getting too active, can we prevent that cell death or can we move it back to happening at the right time? So one set of possible therapies is to control the activity of those inhibitory cells. Can we keep them active or prevent them from being too active? The flip side is, we think something's making those cells die. We think it's that the other cells, the excitatory cells, are too active. So if that's the case, then we can try to dampen the activity of those cells.

And you can do that with drugs, like commonly used anticonvulsants kind of have that effect. And then you can ask if we can save these cells from dying or move them to dying at the right time, then do we mitigate the spasms and do we improve outcomes like reduce seizures or reduced to kind of cognitive behavior in the animal.

Kelly Cervantes: I'm curious to hear from you, what is the area of IS research that is the most promising, that you're the most excited about?

Chris Dulla: That's a good question. I think the things that are most interesting to me are... There's a couple of different things. So one is early diagnosis. That's where there's technologies that are not that far away that can identify EEG signals that are abnormal. And the other thing is genetic testing is becoming more and more common, and more and more things can be ascertained from things like blood. Normally, to learn about the brain, you'd have to get brain tissue or what's called cerebral spinal fluid from a lumbar puncture or spinal tap. Those things are not things we want to be doing, so we're realizing now we can learn a lot more about how the brain is functioning from the blood. So there's two kind of really cool, clinically focused directions where early detection would be a huge improvement. The other thing is around drug discovery and finding new targets.

So the reason that we were so excited about our project, and I'll just shamelessly self-promote for a second, is that the protein that I mentioned, which is called beta-catenin, we got excited about it because it seems like it's a central component of how cells function, and that lots of different mutations that come from infantile spasms patients kind of feed into that central pathway. So our dream with this project was, if all of that is correct, and beta-catenin is the central signaling module by which many other mutations act, that we could have a drug that would treat one thing, beta-catenin, but it would be beneficial for lots of kids that had lots of different mutations. And so that's somewhere where I think maybe beta-catenin is the right target for that, maybe it's not, but that idea that there might be kind of central events in brain development that lead to IS that can be targeted for drug discovery, I think is really exciting.

And those are challenging questions, and we ran into some of those challenges in doing this work that if you do have a target that is so fundamental to how cells function, it's often very difficult to manipulate it and not have a lot of side effects. So that's where the personalized medicine part comes into it and where really deep understanding of cell biology and how molecules talk to each other in different parts of the brain are really critical. There's also this other kind of new trend in neuroscience and across biology that's called single cell biology, which means that... You know, your brain is made up of millions of neurons and each one is different, but most of the tools that we use to assay how the brain functions, either we just assay one cell at a time and try to ask a question about that one cell, or we'll take a piece of tissue that is from an animal model and we'll grind it up and measure something in it, and we take all those cells and we mix them together. So we're losing a lot of information.

And so advances in single cell biology have allowed us to use big data and data science along with new kind of engineering approaches to understand every single cell separately. And what we see in things like epilepsy and lots of neurological disorders is that, number one, it's often a very small number of cells that are driving epilepsy, and number two, because all these cells are kind of different from each other, if you understand how each cell works separately, then you can tune that therapy to hit only the types of cells that you're interested in. So that could have big effects for infantile spasms if you take our developing inter neuron idea that... Maybe we somehow figure out a way to get our drug just to target those cells. There's a couple of things that I'm pretty excited about.

Kelly Cervantes: Well, I'm certainly excited about them too, and I know that myself, the community, Cure Epilepsy, we are all just so appreciative of the work that you're doing, the mentorship that you're providing, and the advocacy that you are doing within the epilepsy field. So Dr. Dulla, thank you so much for sharing your expertise and teaching us about your lab today and just know that we're eternally grateful.

Chris Dulla: You're very welcome and thank you and everything you do for epilepsy community as well in this podcast. I think a lot of people watch it and love it. So thanks for all your work on that.

Kelly Cervantes: Thank you, Dr. Dulla, for sharing your research and insights on infantile spasms, and thank you for the work that you and your team do to improve our understanding of IS. As Dr. Dulla mentioned, Cure Epilepsy has been at the forefront of infantile spasms research, beginning with its infantile spasms initiative launched in 2013 with \$4 million in funding. IS continues to be an area of focus for Cure Epilepsy as a member of the Infantile Spasms Action Network or ISAN. If you have questions about infantile spasms or concerns that your child may be displaying signs of IS, visit the ISAN website at www.infantilespasms.org. Cure Epilepsy, inspiring hope and delivering impact. Thank you.

Legal Disclaimer: The opinions expressed in this podcast do not necessarily reflect the views of Cure Epilepsy. The information contained herein is provided for general information only and does not offer medical advice or recommendations. Individuals should not rely on this information as a substitute for consultations with qualified healthcare professionals who are familiar with individual medical conditions and needs. Cure Epilepsy strongly recommends that care and treatment decisions related to epilepsy and any other medical conditions be made in consultation with a patient's physician or other qualified healthcare professionals who are familiar with the individual's specific health situation.