Alison Lafferty

Hi, my name is Alison Lafferty, I'm currently in Nevada, and I suffer from stiff-person syndrome. So I was diagnosed on November 18th, 2021 after almost two years of searching for a diagnosis. I started out going the orthopedic route because my symptoms were tightness in my back, spinal type pain, heaviness in my trunk area, and pain that went down my legs when I would walk. I went to the orthopedist and they ran every test under the sun that they could do, X-rays, MRI, CTs. And from their standpoint, I was completely healthy. And I remember walking out of every single appointment with tears streaming down my face because I knew something was wrong but I was being told that I was fine. And a lot of people will be like oh I know, I've been gaslit like that before. And I will have to say they were great, they were wonderful. I never felt like they were telling me I was crazy. They were being honest and that from an orthopedic standpoint, I was fine.

Orthopedic said we don't know what else to do, we're going to refer you to neurology. I was lucky enough to get a doctor who was European. Why I say that is because in Europe stiff-person syndrome is studied a little bit more in medical school than it is here. He said you're presenting with some signs of something called stiff-person syndrome, I doubt you have it, it's so rare but I wanna test you for it. And so I'm gonna run a GAD65 test. And I'll always remember October 31st, 2021, I got the test results back and the GAD65 counting limit has a cut off at 25,000 and mine was 25,000. I initially thought this is just my diabetes because GAD65 can also test for diabetes. I called the office, said hey, do you think I can get in a little earlier to discuss these results? They've both got red flags next to them, what's going on? She calls me back and says your test results are fine, you're totally fine, we'll see you in two weeks for your EMG. Because we had already set that up.

I walk in and the doctor goes, I'm so sorry. And I looked at him and I was like what are you talking about? Like literally why are you looking at me with the saddest eyes? He goes, the nurse didn't tell you? Like you have stiff-persons. And I remember we had to reschedule the EMG because I was just racked with sobs. And for that you have to stay pretty still. So first thing I do at 23 years old is call my mom and I go hey, do you remember that test that we were like there's no way I have this? I have it. And I just remember my mom was silent and she was like I'm gonna go get your dad. My dad came on the phone and I remember just crying. There were no words, it was just crying. And I hung up, I went home. My husband worked on the range and for people who are not familiar with the military, this meant like there was no way I could text or call him. But I waited until he got home. And I remember I was just like red, blotchy eyes. And I told him and he was like whoa, I thought the nurse said you didn't have it.

About a month later they sent me to MUSC, the Medical University of South Carolina, where I was hospitalized for a week to try IVIG. It worked. It is very similar in its side effects to chemo and radiation. You feel sick, you feel nauseous. The only difference is there's really no like physical changes. I was there for about a week. Then I went outpatient and they said well we need to make sure that there's nothing in your brain at all before we continue IVIG. So I had an angiovenogram where they stick a little tube through your thigh and go all the way up to your brain. And to this day, it was the most painful experience of my life. And then after that, I went on to home infusions. And I was on home infusions until November when I found out I was pregnant. And that was not planned but pregnancy relieved a lot of the symptoms. Had my daughter in July of '23 and was essentially symptom free for about six more months after that before all the symptoms came barreling back.

	The thing that I really wanna touch upon is the symptoms that led me to the orthopedic and later the neurologist. In July of 2021, I was in Charleston, South Carolina and I had walked half a block maybe, not even a full block and my full body went stiff. My husband ran to go get the car and he literally had to like bend my knees for me to get me in the car and like relax because I couldn't move. And we weren't sure if he did that if he would end up like snapping my knee. Trunk pain, leg pain, it eventually radiated up my back, down my arms, into my hands. And the best way I can describe it is it feels like you have weights on your hands and feet at all time, like you're just carrying them around. When I have to use pencils or cook or use anything that uses fine motor skills, my hands like balloon, they swell and sometimes they'll kind of sit in that claw position. And you could try your hardest to get them to come out of it you just gotta let it happen.
	Charley horses multiplied by 10 is how I would explain the spasms that a lot of us in the stiff-persons community have. I get them particularly in my legs and my feet. All that is to say that I am on the very low end of the spectrum in terms of severity. And I feel like that really says something because any healthy person or someone who doesn't know a stiff-person, even people with other chronic illnesses who don't know what stiff-persons is will hear this and go that's the low end of the spectrum? Like I can't imagine the high end of the spectrum. Some doctors will label it terminal but most terminal diseases they'll give you a 'oh you have six months to live', 'oh the average time is so and so'. With this there is none of that. It's just don't know when it's gonna get you but it's probably gonna get you. Right now I'm still on IVIG. I'm very lucky I haven't had to move to rituximab which is a type of chemo drug or plasmapheresis which is a type of very similar to dialysis.
	But at some point, I do know IVIG will stop working, my oral medications will stop working. Unless a cure or an actual treatment for this is found, everything will stop working at some point and I will continue to progress. I was told from the get-go expect at some point to be fully in a wheelchair. I expect to use a shower chair, expect to need an at home nurse. And there are people right now living with this disease that have those things, that are living with those things. And so that's my story. It is not the story of stiff-person syndrome. It is a spectrum disease, it is different for every single person who gets diagnosed. Everybody who is in the community believes that it is very, very much underdiagnosed. And so that's the goal of this is to get advocacy out there. I think it's imperative that people do their research, they check out the National Organization for Rare Diseases to not only learn about stiff-persons but other rare diseases that deserve the recognition and scientific backing that more common, more popular diseases have. So yeah, that's my story.
TPWKY	(This Podcast Will Kill You intro theme)
Erin Welsh	Alison, thank you so much for sharing that story with us. We appreciate it. And for reaching out to us in the first place, like we just... Yeah, thank you.
Erin Allmann Updyke	Yeah, thank you. It was so amazing to get to have the conversation that we had with you and we really, really appreciate you sharing your story with us and with all of our listeners. So thank you for taking the time.
Erin Welsh	Yes. Hi, I'm Erin Welsh.
Erin Allmann Updyke	And I'm Erin Allmann Updyke.
Erin Welsh	And this is This Podcast Will Kill You.
Erin Allmann Updyke	And today we're talking about stiff-person syndrome.

Erin Welsh	Which you may have heard of more recently because of the Celine Dion documentary that came out a few months ago, 'I Am Celine Dion'. I am not Celine Dion, that is the name of the documentary.
Erin Allmann Updyke	The name of the documentary.
Erin Welsh	And we've also gotten some requests from listeners to cover this.
Erin Allmann Updyke	Yeah. I think one of the things... So stiff-person syndrome is an incredibly rare disorder and we've covered some rare disorders that are categorized as rare disorders on the National Organization for Rare Disorders, which we'll talk more about later, on this podcast before. But the thing about a lot of rare disorders is that no one has heard of them because they are so rare. And that is very true or was very true for stiff-person syndrome. I am a physician in medicine and I had not heard of stiff-person syndrome until I think it was 2022 or early 2023 when Celine Dion came out and said that she had been diagnosed with stiff-person syndrome. And I, like most of us, started googling it to try and figure out what it was. And so I think that one of the things that we are looking forward to in this episode is kind of diving into that idea of like what does it mean to have a rare disorder?
Erin Welsh	Right.
Erin Allmann Updyke	And specifically stiff-person syndrome. And a little bit more details about what is this syndrome? How does it work? What kind of symptoms does it cause? And as much as we can about this truly horrific disease.
Erin Welsh	Yeah. Yeah. And yeah, I think that this has given us an opportunity to kind of take a bigger picture at rare disorders which are incredibly varied among themselves.
Erin Allmann Updyke	Yeah.
Erin Welsh	It's not like all rare disorders are the same thing.
Erin Allmann Updyke	Right.
Erin Welsh	But there are certain experiences that are common among rare disorders. And I think that's given us this sort of opportunity to explore that.
Erin Allmann Updyke	Yeah, yeah.
Erin Welsh	But before we get into all of those things-
Erin Allmann Updyke	Before we get into all that-
Erin Welsh	It's quarantini time.
Erin Allmann Updyke	It sure is. What are we drinking this week, Erin?
Erin Welsh	We are drinking A Stiff Drink.

Erin Allmann Updyke	We sure are.
Erin Welsh	We sure are.
Erin Allmann Updyke	We could drink nothing else.
Erin Welsh	Yeah. And it basically is a paper plane, which if you don't know what that is because I had heard of it but had to Google it, it basically contains bourbon, amaro, and aperol. So it's like a spirit-
Erin Allmann Updyke	Spirit-heavy.
Erin Welsh	Spirit-only cocktail.
Erin Allmann Updyke	And we'll post the full recipe for that quarantini as well as the non alcoholic placeborita, better bet we could do it, on our website thispodcastwillkillyou.com and all of our social media channels.
Erin Welsh	On our website you can find all sorts of things from transcripts to links to Patreon, links to merch. We've got some great merch coming up. Links to bookshop.org affiliate account, Goodreads list, links to music by Bloodmobile, an about us page, a contact us form if you're interested in having us give a talk or workshop.
Erin Allmann Updyke	Hit us up.
Erin Welsh	Reach out to us, hit us up. And there's also a submit your firsthand account form. There's a lot of things that you can-
Erin Allmann Updyke	So many things.
Erin Welsh	You can seek out and find on our website.
Erin Allmann Updyke	Thispodcastwillkillyou.com, check it out.
Erin Welsh	Check it out.
Erin Allmann Updyke	Also double check while you're, I don't know, on your internet service provider that you are subscribed to your podcast catcher app, whichever one that you like to use. And if you haven't, take a minute to smash that subscribe button and maybe even give a rating or a review because it really helps us out. So thank you so much for doing that.
Erin Welsh	It does. I can't believe you said "smash that subscribe button".
Erin Allmann Updyke	Isn't that what they say on YouTube?
Erin Welsh	I think it is. I just don't know if I've ever-
Erin Allmann Updyke	My kid watched these really ridiculous YouTube and they're always like "smash that subscribe!" and I'm like we really probably shouldn't let you watch this.

Erin Welsh	Smash that subscribe button. That's amazing. I don't think there's any other business, so let's take a break and then get started.
TPWKY	(transition theme)
Erin Allmann Updyke	As an incredibly rare disease, unsurprisingly we do not fully understand the biology of stiff-person syndrome. But I'm going to tell you everything that I learned in all of the papers that I read and what it seems like we know in medicine thus far. Based on what we know about stiff-person syndrome, it's very likely that this is an autoimmune disorder, meaning that it's something where your body is making antibodies that attack your own cells. And we've covered quite a few autoimmune disorders on this podcast before. We've covered lupus and MS, celiac disease, there's probably more that I'm forgetting. But for this episode, what I want to start with is actually what stiff-person syndrome looks like, what the symptoms are, and what happens to people who have stiff-person syndrome. And then after that get a little bit more into the nitty gritty of how we think this happens. So let's get started. The name stiff-person syndrome, and Erin, I'm sure that you're going to talk a little bit more about how this name came to be-
Erin Welsh	Yeah. Yeah.
Erin Allmann Updyke	But in some ways it's an accurate description of what is happening in this disorder. The stiffness in the name comes from rigidity of the muscles. And this is most often muscles in the trunk, so your torso and your upper legs, but sometimes also the arms and really it can be any muscle. Muscles in your face, muscles in your hands, muscles in your feet. In the trunk, meaning again the core of your body, you get the stiffness both in the abdominal muscles on the front side and the paraspinal muscles, so the muscles on either side of the spine, and especially in the lower back and sometimes extending down into the upper legs as well. And what's happening in this stiffness is that the muscles are firing. So the muscle fibers are continuously contracting without you trying to contract them. These are voluntary muscles, right, meaning that you have to move them voluntarily. But in stiff-person syndrome, they are contracting without voluntary movement even when you're trying to be at rest or trying to relax. And they can become so contracted that it becomes over time difficult, if not impossible, to do things like bend over.
	And this process is often described in stiff-person syndrome as insidious, meaning it's not that somebody wakes up one day with muscles that are so tense they can't reach down and touch their toes but it's a gradual stiffening process. And early on it's often kind of waxing and waning in severity. So some days might be more stiff, some days might be less. But progressively over time these muscles contract more and more and become more and more stiff. But on top of that kind of progressive stiffness, what we also see are these episodic spasms where muscles contract all at once. So the way that I think of this, to make everyone kind of understand what that means, is like picture a charley horse. Because I think we've all had charley horses at some point in our lives, right? Usually when we get a charley horse, it's like you're laying in bed, you're probably dehydrated, you stretch out your leg and all of a sudden your calf muscle just seizes up, right.
Erin Welsh	Yeah.

Erin Allmann Updyke	It's horrible, you yell out in pain. And there's not really much that you can do, right? You have to either just kind of wait it out. You can try and stretch it out, though sometimes it makes it more painful or just seize up even more. So you just have to kind of wait it out and eventually that muscle will relax. In stiff-person syndrome, those kind of muscle spasms can happen but it's not just in say your calf, these can happen in any and all muscle groups and especially they happen in the legs but in multiple muscle groups at the same time. And they're not just happening because somebody is dehydrated and resting in bed and move their leg. They can happen at any given moment but seem to happen especially in relation to things like unexpected noises, unexpected touch, like say you bump into a coffee table that you didn't mean to, also emotional upset, so major stressors, or rapid movement. So imagine like getting out of a car and a bike swerves up, so you have to jump back. Something like that could trigger one of these spasms.
Erin Welsh	And so the spasm is like the intensity of that, like the strength of that contraction and the not irreversibility of it but just like how long it is contracted? Or is it that plus the readiness to contract?
Erin Allmann Updyke	It's both. And so it's that they contract very forcefully but the other thing that's notable about these spasms, and like you said, they happen very readily, just kind of out of the blue. But the other thing that's happening is that so all of our muscles, like all of our limbs and things, you have two sets of muscles for most movements, they're called an agonist and antagonist. So if you think of bending your knee, right. To bend your knee, you have one set of muscles that helps you to bend it and you have another set of muscles that helps you to flex it or to extend it, right.
Erin Welsh	Okay, yeah.
Erin Allmann Updyke	So one for flexion, one for extension. So in the charley horse example, there's just one set of muscles, just your calf muscle is contracting. But what's happening in stiff-person syndrome is that both sets of muscles, if you're talking about maybe spasms happening in your legs around your knee, for example, the muscles to flex your knee and the muscles to extend your knee, they all contract at once. You have agonist and antagonist spasm. And that is what creates that rigidity, that super, super stiffness.
Erin Welsh	Okay.
Erin Allmann Updyke	And it's not like this happens in just say one knee at a time. What can often happen is that these spasms might start with one muscle group but then they kind of progress to encompass multiple muscle groups, even potentially somebody's whole body. And I think if anyone did watch the Celine Dion documentary, there was a really, really horrific moment in that where you see her go into one of these muscle spasms and you can really visualize just how rigid and stiff all of her muscles become during this.
Erin Welsh	I feel like I'm really trying to not ask the 'why?' yet.
Erin Allmann Updyke	I know, I know.
Erin Welsh	Are there other situations in which both sets of muscles or both muscles spasm in that way? So like the charley horse, as an example, it's just one of those muscles.
Erin Allmann Updyke	Yeah.
Erin Welsh	But what else do both sets of muscles contract forcefully?

Erin Allmann Updyke	Yeah, they shouldn't be.
Erin Welsh	Yeah.
Erin Allmann Updyke	They shouldn't be.
Erin Welsh	Okay.
Erin Allmann Updyke	It's not a type of contraction pattern that happens in typical voluntary muscle movement. It is abnormal.
Erin Welsh	Okay. Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	And this is voluntary muscles only where this happens?
Erin Allmann Updyke	So no, not necessarily.
Erin Welsh	Okay.
Erin Allmann Updyke	This can happen in any of your muscles. So we'll get a little bit more into this when I talk about the kind of what we know of the pathophysiology. But this is a neurologic disorder and so this has the potential to affect more than just your skeletal muscles. But it does primarily affect your skeletal muscles, which means the muscles that control your limbs, that control your trunk, that control your breathing, and things like that.
Erin Welsh	Wow. Okay.
Erin Allmann Updyke	Yeah. But so that is why you end up with such profound stiffness is because of how quickly this is happening, how strongly these contractions are happening, and that they're happening in multiple sets of muscle groups all at the same time. And what this leads to is people not being able to move which also means that they can't react. So this can lead to things like falls because people stiffen up and then are unable to right themselves or catch themselves, which is potentially very dangerous especially if you think of the scenario that I mentioned, like trying to get out of a car or something like that. And if you have a spasm in a moment like that or trying to walk down the stairs. And these spasms are quite painful. I mean think of how painful a charley horse is. These spasms can be similarly painful where it is painful to have a muscle spasm and you're having spasms in multiple muscle groups at the same time.
	Stiff-person syndrome is a progressive disorder so if untreated, it does tend to get worse, both in terms of that progressive overall stiffness which we see again, mostly in the trunk muscles and a little bit in the legs as well. But also in these spasms, whether they're becoming more frequent or just more powerful, more unpredictable, whatever it might be. In terms of most severe outcomes, of course people can have very severe outcomes if they have falls during these muscle spasms. But you also can have spasms in muscles including the muscles used for things like breathing. So while it is rare to have spasms severe enough to cause respiratory distress or death, it can happen and it has happened. So stiff-person syndrome is a very rare and potentially very life threatening disorder depending on the scenario. So when it comes to, Erin, I know the questions that you have that are burning of like why and how on earth something like this happens.

Erin Welsh	Yeah. Right. I'm like is this like tetanus at all? Is it the same sort of like... Yeah.
Erin Allmann Updyke	I'm glad that you mentioned tetanus because there are some similarities with tetanus, especially in terms of what these symptoms can look like. So these spasms can look a lot like tetanus.
Erin Welsh	Okay.
Erin Allmann Updyke	But what I first want to say before I get into the pathophysiology, and I swear I am getting there, is that all of this description of stiff-person syndrome is what is often called kind of classic or typical stiff-person syndrome. There are also other types of stiff-person syndrome that have been described and sometimes SPS, I'm going to call it SPS a little bit, is considered a spectrum disorder. So some of the other types include something called stiff-limb syndrome which as the name suggests is very similar but tends to begin or be mostly focal to one limb, like an arm or a leg or something like that, which may or may not become more widespread. There's also something called, it's a long name, progressive encephalitis with rigidity and myoclonus. It has an acronym, it's PERM.
Erin Welsh	Okay.
Erin Allmann Updyke	And this is a similar disorder but that is often a lot more rapid in onset rather than this very insidious, slow onset. And it tends to have more brainstem involvement. Most of what I talked about with classic SPS, it's really like muscles, it's really like your peripheral muscles that are being most affected. But with some other types of SPS, including a non classic SPS and PERM, you can see more of brain stem involvement. So you might see more things that look a little bit more like Parkinson's than classic SPS. And then finally there are also types of SPS disorders that are associated with certain cancers. But what I'm going to focus on, because what we know the most about in terms of the pathophysiology, is the more classic stiff-person syndrome. Okay? But know that this doesn't necessarily encompass everyone who has a stiff-person spectrum disorder.
	So I mentioned already that this is most likely, and I say most likely because we don't fully know, an autoimmune disease. So we are making antibodies against our own cells instead of antibodies against a virus or a bacteria or whatever, or in addition to those. In most cases, like 60%-80% depending on the paper that you read, the autoantibody that's involved here is against something called GAD, specifically GAD65. So we're going to get deep into what the heck these things mean. GAD or glutamic acid decarboxylase is an enzyme. This enzyme is present in our nervous system and our pancreas but we're going to ignore that for now.
Erin Welsh	Okay.
Erin Allmann Updyke	We'll get there. And in our central nervous system and our peripheral nervous system, GAD's job is to make something called GABA. Like Yo Gabba Gabba. I feel like we've talked about GABA before.
Erin Welsh	Yeah.
Erin Allmann Updyke	On our alcohol episode probably.
Erin Welsh	Yes.

Erin Allmann Updyke	GABA, which is short for gamma-aminobutyric acid, is a neurotransmitter which means it's a chemical messenger that our brain and our nervous system is using to send signals so that our nerves can do their job. For example, so that our nerves can talk to our muscles to tell them to contract or relax. That's what neurotransmitters do, as one example. GABA is an inhibitory neurotransmitter which is a fancy way of saying that GABA tells our body to chill. In our brains and in our nervous system, GABA goes uh oh, you need to calm down, you're being too loud, you need to just stop. Like can you just not? That was a quote from Taylor Swift.
Erin Welsh	Oh my god.
Erin Allmann Updyke	Anyways. So that is what GABA is doing. GAD, this enzyme, is what makes GABA and GABA is what tells us to chill out. So in stiff-person syndrome, you're making antibodies that are targeting GAD. So you're screwing up this enzyme so then you cannot make GABA. So you can't calm down. Your nervous system can't just stop. So what's happening is that your muscles are getting uninhibited excitatory signals with no ability to inhibit them. So that results in spasm, continuous contraction, and stiffness. Now I know one of the things you're going to ask, because you probably have a lot of questions, but one of the big questions then is why then is this a waxing and waning phenomenon?
Erin Welsh	Right.
Erin Allmann Updyke	And why do we see the stiffness in these spasms in relation to certain triggers and not just all the time, especially at first?
Erin Welsh	Right.
Erin Allmann Updyke	Well let me tell you. It's at least in part because in our nervous system we have two different kinds of this enzyme, GAD. We have one called GAD67 which makes basal levels, which means a little bit all the time of GABA. So we have some GABA floating around. And then we have one called GAD65. And GAD65 makes GABA just as needed. Whenever we have some kind of excess excitement like times of stress where our nervous system gets over excited and is sending too many signals, then GAD65 makes GABA just to be like whoop, calm it down, bring it back down.
Erin Welsh	Okay.
Erin Allmann Updyke	So in stiff-person syndrome, we make antibodies just against this GAD65, not 67. So you have production of this all the time GABA but you don't have or you have very limited production of this as needed GABA, which is perhaps why we see these spasms in relation to those triggers like times of stress, etc.
Erin Welsh	But why? Do we know anything about the initial trigger that causes these first antibodies to be produced? Like it just seems like why?
Erin Allmann Updyke	Erin, that is the actual million dollar question, right.
Erin Welsh	Yeah.
Erin Allmann Updyke	So we believe that nearly all autoimmune diseases are both genetic, there's a genetic predisposition, and then there's some kind of environmental trigger.
Erin Welsh	Right.

Erin Allmann Updyke	Be that an infection, be that an exposure. We don't know what either are in this case. We don't necessarily know or haven't pinpointed what specific genes might be most strongly associated with stiff-person syndrome. And we also have no idea what the trigger could be. Could it be infectious? Maybe. Could it be some type of exposure? Who knows? We do not know. What is the first trigger? Why do some people start making these antibodies? We have absolutely no idea in the case of stiff-person syndrome.
TPWKY	(transition theme)
Erin Welsh	Okay. So I have a question about GAD65.
Erin Allmann Updyke	Yeah.
Erin Welsh	I know you said it's like as needed when times are stressful but like can you tell me more about what those times look like? Like what does that actually mean? How long are those times? Short periods of time? Is it on the order of seconds to like days?
Erin Allmann Updyke	I have absolutely no idea the answer to that question.
Erin Welsh	Okay, okay.
Erin Allmann Updyke	Yeah.
Erin Welsh	And so like on a day to day basis, are you producing GAD65?
Erin Allmann Updyke	Yeah. So GAD65 is there all the time.
Erin Welsh	Okay.
Erin Allmann Updyke	Like you and I, we've got GAD65 all the time. We've got it in our pancreas, we've got it in our nervous system, and we're using it all the time.
Erin Welsh	Okay.
Erin Allmann Updyke	At any given moment, you're probably using it.
Erin Welsh	Right.
Erin Allmann Updyke	You are getting like, I don't know, you get stressed about a work deadline, you're definitely using it. You're going out for a run and you see something that is novel, you're probably using it. It's there all the time. You've got GABA and other excitatory... GABA is inhibitory. You've got both excitatory and inhibitory neurotransmitters floating around all the time, all the time.
Erin Welsh	Okay.
Erin Allmann Updyke	Yeah. So what's happening here is that you just have an overall reduction in GABA and you're not able to then produce it in this as needed basis. And again, we don't fully understand because there's a lot more that's complicated about this.
Erin Welsh	Yeah.

Erin Allmann Updyke	Here are some of the things that make it more complicated. Number one, GAD65 is not the only autoantibody that we see in stiff-person syndrome.
Erin Welsh	Right.
Erin Allmann Updyke	There are actually six different autoantibodies so far that have been characterized that are present in people with stiff-person syndrome or stiff-person spectrum disorders, like those ones that I mentioned earlier. The other ones are also against either related neurotransmitters or related receptors, like even the GABA receptor itself or other related receptors that are present at this synapse where your nerves are talking to your muscles and sending these signals. But on top of that, some people with stiff-person syndrome are antibody negative entirely.
Erin Welsh	Right.
Erin Allmann Updyke	Which means we either haven't identified the autoantibody that they have that's causing damage or they're having these exact same symptoms by some different as yet to be described mechanism. So then that begs the question. We have this possible explanation, right, we know what GAD65 is doing, we know what happens in mice models, etc, when we have autoantibodies against GAD65. We have a lot of data to support what we think is going on in the case of GAD65-associated stiff-person syndrome. But this disorder is bigger than that. And so we really don't fully understand it. And like you mentioned, we do not know what the triggers are for why somebody makes these antibodies.
Erin Welsh	Okay. But the end result is more or less, for classic SPS, is more or less the same with these muscle spasms and rigidity. And so it's like something likely along that pathway to-
Erin Allmann Updyke	Exactly.
Erin Welsh	That blocks the production of GAD65. Or something like that. Although-
Erin Allmann Updyke	That blocks the production of GABA.
Erin Welsh	GABA.
Erin Allmann Updyke	And GAD65. Yeah.
Erin Welsh	Okay. So many acronyms, Erin.
Erin Allmann Updyke	Too many acronyms, I know, I know.
Erin Welsh	I can't keep up with it.
Erin Allmann Updyke	Yeah.
Erin Welsh	Has stiff-person syndrome been observed in other species?
Erin Allmann Updyke	I read one thing that said it has been seen in a horse.

Erin Welsh	Okay.
Erin Allmann Updyke	And I know that we have induced it in mouse models in a lot of studies.
Erin Welsh	Right.
Erin Allmann Updyke	But I don't know in terms of naturally occurring in other animals, I didn't look deep into it. So the only one that I saw was that it seems like maybe there's something similar that has happened in a horse.
Erin Welsh	Okay. Erin, I have two other questions.
Erin Allmann Updyke	Okay.
Erin Welsh	One, you mentioned pancreas and the other, I know that you mentioned cancer and you were like we're not going to talk about cancer associated with stiff-person syndrome.
Erin Allmann Updyke	Yeah.
Erin Welsh	But I kind of would like to know just a little bit more about that.
Erin Allmann Updyke	Yeah. So okay, so I'll address the cancer question first. Some cancers, and this is true, this is not stiff-person syndrome specific but some cancers can cause, there's a fancy name for this, they're called paraneoplastic syndromes. So it basically means your cancer starts doing weird things. And your body, in trying to attack it, starts making things that then end up hurting your body further in a way that's not the cancer directly. Right.
Erin Welsh	It's like throwing the kitchen sink or like...
Erin Allmann Updyke	Exactly.
Erin Welsh	But also you're throwing the baby out with the bathwater from the kitchen sink.
Erin Allmann Updyke	Bathwater? Sure, yeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	Let's use both those analogies.
Erin Welsh	Something like that, yeah.
Erin Allmann Updyke	So what we see sometimes in some types of... It seems like breast cancer is one of the strongest associations and some types of lymphoma I saw as well. There are some people who have developed very similar symptoms to stiff-person syndrome and it's found that they have these autoantibodies usually against something called amphiphysin. In any case, it's autoantibodies against a neurotransmitter that cause symptoms very similar to stiff-person syndrome but as a result of the cancer itself, if that makes sense.
Erin Welsh	Right.

Erin Allmann Updyke	It's very, very rare even among cancers, it is incredibly rare. I don't even have statistics on it. It's like it has happened but it is not something that is common with cancers.
Erin Welsh	Okay.
Erin Allmann Updyke	Including breast cancer which is very common. And then you asked about the pancreas.
Erin Welsh	Yes.
Erin Allmann Updyke	So this is another way that the story of stiff-person syndrome is more complicated and it's because of GAD. So GAD and specifically that GAD65 is not only present in our nervous system, it's also present in our pancreas, specifically in the cells that make insulin. So we actually see the same type of autoantibodies, that is antibodies against GAD65 in type one diabetes. That is one of the ways that we diagnose type one diabetes. And we can also see very similar autoantibodies in some other neurologic disorders as well. And this is where that ultra super hyper specificity of antibodies comes into play in a way that we've only kind of briefly mentioned in the past. So if you think of this enzyme GAD, GAD65, as a chunk of LEGO, I imagine it as one of those six or eight LEGO blocks. You know like the long ones? The autoantibodies that you're making are like a little square LEGO and they're only attaching to one section of that enzyme.
Erin Welsh	Okay.
Erin Allmann Updyke	So the ones that you make in type one diabetes attach on one side of the GAD65 LEGO and the ones that you make in stiff-person syndrome attach on the other side of that LEGO, even though they're attacking the same enzyme.
Erin Welsh	So there's room for both.
Erin Allmann Updyke	Exactly. Yeah. And so we do see, because there is crossover, we do see an association between stiff-person syndrome and type one diabetes. About 30%-35% of people with stiff-person syndrome also have type one diabetes, though only about 1 in 10,000 people with type one diabetes have stiff-person syndrome.
Erin Welsh	But everyone who has type one diabetes produces antibodies against GAD65.
Erin Allmann Updyke	GAD65 is one of the major antibodies in type one diabetes.
Erin Welsh	Interesting.
Erin Allmann Updyke	Yeah.
Erin Welsh	But all of this, like all of the complicated and the fact that we don't still know like the root cause or there might be multiple root causes, like how does that affect then treatment prospects?
Erin Allmann Updyke	Such a good question, Erin. So in terms of treatment, we don't have a lot.
Erin Welsh	Right.

Erin Allmann Updyke	But it does get even more complicated if you have someone who, say, you can't identify any autoantibodies. Because then you're wondering is this truly autoimmune or not? Are there symptoms going to respond to immune modulators the same way that we might use for somebody who has these identifiable autoantibodies? But so that is one of the big things that we can use in treatment. It's something called IVIG which is probably interesting enough to do a whole episode on, Erin.
Erin Welsh	All right, let's do it.
Erin Allmann Updyke	It is really, really interesting. It's basically really, really high doses in this case of pooled antibodies from literally thousands of people.
Erin Welsh	Right.
Erin Allmann Updyke	And you're giving people antibodies and in the case of an autoimmune disorder, it ends up paradoxically kind of reducing that person's own atypical autoimmune response. The problem is antibodies, you're giving them antibodies to help deal with their antibodies. It's so interesting and weird.
Erin Welsh	Yeah. Is there a way to produce IVIG in a lab setting or do we still need to get it from people?
Erin Allmann Updyke	Yeah. As far as I know, it's still collected from people and pooled from thousands of donors so that you have a really huge variety of it. It's not like a monoclonal antibody which we can make in a lab-
Erin Welsh	Right.
Erin Allmann Updyke	That is one specific kind of antibody. And there are some, one specific type of monoclonal antibody called rituximab that some people sometimes use for stiff-person syndrome because that targets the cells that make antibodies in your body. It targets some of your B cells.
Erin Welsh	Okay. Interesting.
Erin Allmann Updyke	Yep. But those treatments aren't necessarily the first line that's offered to everyone with stiff-person syndrome. Often the first line of treatments are medicines called benzodiazepines, which is things like Ativan, Valium, Xanax. If you've heard of those, those are the common names. I feel like everyone's heard of Xanax. Valium is the one that's most commonly used because it has a bit of a longer mechanism, blah, blah, blah. And I want to talk a little bit more later about benzodiazepines in relation to stiff-person syndrome because I think that they have created this really interesting kind of problematic paradox. But they are very effective in a lot of cases at treating the symptoms of stiff-person because the mechanism of benzodiazepines is they act like GABA. That is what they do in our brains.
Erin Welsh	Right.
Erin Allmann Updyke	So they aren't GABA but they act at the same receptors. And so if you're not making enough GABA, we're basically giving you replacement GABA. So those and then other types of muscle relaxers that are used to treat those spasms that we also use for spasms in other conditions as well. Those are kind of the main types of treatments that we have thus far. None of them fundamentally change the course of the disease. None of them come close to approximating a cure.

Erin Welsh	Because there isn't like one autoantibody that you're looking for, is diagnosis primarily based on symptoms?
Erin Allmann Updyke	Yeah, it's what we call a clinical diagnosis. So there's not like one single test that you can do to kind of clinch the diagnosis. It's a combination of those symptoms, the stiffness especially in the abdomen and the spine and the trunk, the spasms that we see, especially having them be triggered by specific things like noises or stress or a touch or something like that. You can do the antibody testing and if that's positive, that's really helpful. If it's negative, it might not be that helpful. But then there also are tests that you can do called EMG which is electromyography and that's actually testing your muscles. And what we see is continuous activity of those muscles again in both those agonists and the antagonist muscles. So you're looking at multiple muscle groups and you're seeing continuous activity even when the person is at rest.
	And then some people say that if there is a good response to benzodiazepines, that's also helpful though it isn't technically part of the diagnostic criteria. And then also just ruling out other things that might be more common neurologic disorders that you might have other additional symptoms. Like for example, Parkinson's causes a lot of stiffness and can cause spasms sometimes. But then you also expect to see other things. You expect to see tremor, you expect to see MRI findings maybe, etc. So there might be a whole battery of tests that someone has to undergo and there's often really significant delays in diagnosis.
Erin Welsh	Yeah.
Erin Allmann Updyke	Very often this can be misdiagnosed as a primary psychiatric disorder, something like anxiety, depression, phobias.
Erin Welsh	I'll talk about it.
Erin Allmann Updyke	Yeah. We'll talk more about that later. But it's a huge problem.
Erin Welsh	It is.
Erin Allmann Updyke	But that is stiff-person syndrome and what we know about the biology of it.
Erin Welsh	It's a lot.
Erin Allmann Updyke	It's a lot. And it's a really... I think that in the next, I hope I guess that in the next 10-15 years, I'm jumping ahead but I really hope that we learn so much more about the different types and about like what the underlying mechanisms are and what the triggers really are for these autoantibody productions in the first place.
Erin Welsh	Yeah, I mean I feel like it seems like we know a lot but there's still a lot that we will need to get figured out but hopefully that will happen.
Erin Allmann Updyke	Yeah. And I always wonder how much are we going to be wrong about?
Erin Welsh	Right.
Erin Allmann Updyke	This is what we think we know and might be true for a good proportion of people. But it's such a big umbrella it seems like. So what are we missing and what are we wrong about so far?

Erin Welsh	What's underneath the stiff-person syndrome umbrella that will not be in 15 years?
Erin Allmann Updyke	Exactly. Yeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	Well Erin, along that line, how did we get to where we are today? When did we first find out about this? Tell me everything you know.
Erin Welsh	I will do that right after this break.
TPWKY	(transition theme)
Erin Welsh	We've said this 1000 times. Stiff-person syndrome is a rare disease. To be classified as a rare disease, the condition has to affect no more than 1 in 2000 individuals, that's in the EU, or 1 in 1250 in the US. And maybe those numbers have changed slightly, I'm not sure. This is from paper from maybe nine years ago. And I know that you're going to talk a lot more about numbers later in the episode. But for some perspective, stiff-person syndrome affects 1-3 individuals per million which is very much a rare disease.
Erin Allmann Updyke	Yep.
Erin Welsh	But numbers are only one small part of the rare disease experience. Rare diseases as a group are in fact not that rare.
Erin Allmann Updyke	Right.
Erin Welsh	An estimated 25 million people in the US are living with a rare disease. And while the symptoms or pathophysiology or treatments might be very different among rare diseases, there are some elements that they're likely to share. Diagnostic delays, inappropriate treatments or medical interventions, a disconnect between a patient's needs and a provider's ability to provide them, not being believed, just to name a few. Many of these challenges for the management of rare diseases exist because of what is simply a lack of information about them. Research is less likely to be funded, studies face issues of sample size, and awareness is just of course much lower than for other more common diseases. Over the past few decades, a huge effort has been made across the globe to address some of the challenges facing rare diseases. And I'll talk a bit more at the end of this history section about some of these organizations or legislations and the work that they have done or are doing. But first I want to go through the story of the rare disease that is the focus of today's episode of course, stiff-person syndrome.
	In 1956 a report was published in the proceedings of the staff meetings of the Mayo Clinic by two neurologists, Frederick Moersch and Henry Woltman. And shout out to the Mayo Clinic librarian, like I emailed the librarians to be like I can't find a copy of this online anywhere, can you please send me a copy? And they did. It was thrilling. This report was titled 'Progressive Fluctuating Muscular Rigidity and Spasm ("Stiff Man" Syndrome); Report of a Case and Some Observations in 13 Other Cases'. And it described a series of patients who experienced muscle cramps, attacks of muscle tightening, muscle rigidity and spasms, often preceded by a sudden voluntary movement. The first of the individuals described was a 49 year old farmer from Iowa who came to the Mayo Clinic in 1924 for quote "muscle stiffness and difficulty in walking". 1924.

Erin Allmann Updyke	Wow.
Erin Welsh	This report was published in 1956.
Erin Allmann Updyke	Wow.
Erin Welsh	So if you're feeling bad that you're sitting on data that you swore you would publish a couple of years ago, like from your PhD dissertation, at least you didn't wait 32 whole years.
Erin Allmann Updyke	Oh Erin, you talking to me specifically?
Erin Welsh	I'm talking about myself.
Erin Allmann Updyke	Yep.
Erin Welsh	But I'm also kidding because a single case report probably wouldn't have been published or gotten as much traction as one that described a new syndrome and had like multiple cases.
Erin Allmann Updyke	Right.
Erin Welsh	And actually there was, to further underline this, in retrospect people picked apart another case report of what was later agreed upon as probably being stiff-person syndrome. It was described by this guy Orenstein in 1935 but no one really talked about it.
Erin Allmann Updyke	No one thought much of it.
Erin Welsh	Yeah, exactly. And probably it was in part because Orenstein concluded that it was my myositis fibrosa at the end of it. But anyway, back to this farmer. So for the previous four years before 1924, he had experienced increasing muscle stiffening that got even worse after a fall in 1923 after which he could not work. Quote: "His muscular condition had worsened, his neck muscles had remained rigid most of the time, and his head could be brought forward only with great effort. Also the abdominal muscles and to a lesser degree those of the lower part of the back and those of the thighs had partaken of the same stiffness or tightness. Moreover the rigidity had been punctuated by intermittent and moderately painful spasms." End quote. So Moersch and Woltman, after examining this person, performed all of the neurological examinations that they could think of but they couldn't come up with a diagnosis. They prescribed warm baths, massages, physical therapy, things that would increase this person's comfort. And that did seem to help. But without knowing what was causing his symptoms, they were powerless to actually treat the root cause. And over the next few years, they kept in touch and the last they heard from him was in 1932. Quote: "The stiffness lessened and muscular spasms were fewer than they had been. He could be on his feet but he was weak and could take only a few steps unassisted." End quote. But this case, even though the last they heard was like decades previously, it stuck in their minds. And as neurologists at the Mayo Clinic which is one of the world's largest and most famous hospitals for treating difficult cases, Moersch and Woltman were in a unique position to observe not just one instance of this unexplained neurological disease but 13 more. Because oftentimes if you're like something is wrong with me, I don't know, you go to the doctor and they're like we don't know, go to this specialist, they don't know, go to this specialist. And then eventually you end up at the Mayo Clinic.
Erin Allmann Updyke	You end up at Mayo. Yeah. Absolutely.

Erin Welsh	And so this 13 more, 14 in total was enough for them to say okay, there might actually be a pattern here. Like these seem to have symptoms in line, there's like a trajectory of the disease that seems like they have in common. And we're going to call this stiff-man syndrome, a name which in their own words, quote, "could not be taken by anyone to be final." End quote. But which nevertheless stuck around for 35 years until it was changed to stiff-person syndrome in 1991. We've talked about the importance of names on this podcast before many, many times and this is no exception. But it does make me wonder whether it was the "man" in stiff-man syndrome that delayed diagnosis for women or if it was just the way that medicine saw and treated women at the time. And I feel pretty strongly that it was the latter. Like I don't think, I'm not in Moersch and Woltman's heads but I don't think that they called it stiff-man syndrome to say only men get this disease.
Erin Allmann Updyke	Right.
Erin Welsh	I think it was just sort of the 1950s.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	1950s, I feel like they just used the word 'man' all the time.
Erin Welsh	Right. It was like instead of humanity, it was just man.
Erin Allmann Updyke	Manity.
Erin Welsh	Instead of person... Yeah, just manity.
Erin Allmann Updyke	Yeah.
Erin Welsh	And to illustrate my point further, I'm just going to read you some snippets from a 1958 article by Richard Asher, a physician in London. The title of the article, 'A Woman with the Stiff-Man Syndrome' has at the end of it a lovely little asterisk that reads, quote, "I cannot avoid the paradoxical title. Stiff-person syndrome might be a better name." End quote. It was 1958.
Erin Allmann Updyke	And it was still like so many years later before they actually changed the name.
Erin Welsh	1991. Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah, yeah. But I think that just goes to show how slowly things can move sometimes in medicine.
Erin Allmann Updyke	Right, right.
Erin Welsh	Like everyone knew that it wasn't just men affected.
Erin Allmann Updyke	Yeah.

Erin Welsh	And it was just like come on, let's make this official.
Erin Allmann Updyke	Yeah.
Erin Welsh	So Asher's case report is unlike any other case report or article that I've come across before. It reads like a story. There's a narrative, Asher uses first person pronouns, there's self reflection, there's humanity, not just manity. Asher starts off the article by describing how he was reading Moersch and Woltman's report when he realized that it sounded pretty familiar. Quote: "They were a clear description of the case of a woman whose extraordinary spasms had puzzled me 10 years previously." End quote. So he tracked her case down. He was like okay, I remember this person, this sounds like she had stiff-man syndrome or stiff-person syndrome. And so he was like let me see if now, like what she's doing these days. It was 10 years ago. And then he retells the story of this woman who had essentially not been believed by anyone and was cast aside as a problem patient for years until her death. And Asher himself was complicit in her mistreatment and he acknowledges this. So after checking into the hospital in 1946 with extremely painful spasms, she was diagnosed by Asher with quote "spasms secondary to spinal arthritis with hysterical overlay". End quote.
Erin Allmann Updyke	Wow.
Erin Welsh	The hysterical part as in it's all in her head and she's doing this for attention, that part would stick with her over the years. That would be on her case forever, all her case notes.
Erin Allmann Updyke	Wow.
Erin Welsh	Two years later, this would be in 1948, she was admitted to a quote "mental hospital with depression and troublesomeness. The latter was shown by attacks of spasm and screaming. A month after admission, she felt her femur snap during a spasm. A later spasm then broke the screw and plate that had been put into her leg. She became a chronic case and stayed for five years in the wards." End quote. All just still thought to be hysterical. In 1955, nine years after her first admission, she checked back into the hospital. The note read, quote, "Condition worsening, hysterical outbursts on little or no provocation becoming worse if soothed, gradually quietening if ignored." End quote.
Erin Allmann Updyke	Ugh.
Erin Welsh	And so Asher after learning of this readmission was like oh wow, I remember this patient and her condition seems the same. I think that there might be something actually like organic going on, like something actually physical going on.
Erin Allmann Updyke	Quote unquote "organic", yeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yep.
Erin Welsh	But the psychiatrist who saw her was like no way, man. Quote: "Whatever her difficulties are, she appears to be completely lacking in insight and therefore psychologically inaccessible. It is obvious that her rehabilitation is a formidable proposition. She appears to have satisfied some emotional need in her illness." End quote.

Erin Allmann Updyke	Oh Erin.
Erin Welsh	And later adding to this, quote, "Very difficult and uncooperative, prefers to stay in bed. As the patient obviously does not want to get better, it is time we realized we have lost this battle." End quote.
Erin Allmann Updyke	Ugh.
Erin Welsh	Four months later, after Asher had come across Moersch and Woltman's paper, he finally succeeded in seeing her and diagnosing her with stiff-man syndrome. Six months after that, at the age of 50, she died unexpectedly after a severe spasm described in the notes as a quote "hysterical turn". Asher notes, quote, "Her hysteria had at least been awarded the posthumous dignity of inverted commas." End quote. So like at the end at least hysterical was in quotes, he's saying.
Erin Allmann Updyke	Wow.
Erin Welsh	And not just as a diagnosis. And I spent so much time on this article because I think it is such a perfect and heartbreaking example of how people with rare diseases, both historically but also today, are often not believed and how you have to wait years for a diagnosis if it ever comes. But I think the other thing that stuck out to me is the remarkable fact of the author recognizing his role in this and changing his perspective.
Erin Allmann Updyke	Right.
Erin Welsh	In the intro he writes that one of his reasons for reporting on this case was quote "because it shows that syndromes are sometimes labeled hysterical for no better reason than that they are not yet officially described, even in this case where the patient's hysterical spasms were so titanic that with their power she bent a Smith-Petersen pin and fractured a steel plate and screws." End quote. So I just really... Like we talk a lot about this period of medicine.
Erin Allmann Updyke	Yeah.
Erin Welsh	And that still has its effects today, the echoes are very present as probably everyone who's listening can attest to not being believed by their doctor, not being listened to. But I think things have gotten better. And I really appreciated reading about like part of the transition of that.
Erin Allmann Updyke	Right, right.
Erin Welsh	This awareness, this self awareness of like oh, I was wrong.
Erin Allmann Updyke	I was wrong.
Erin Welsh	And then writing a case report about it.
Erin Allmann Updyke	Right.
Erin Welsh	And being like I want people to know that this is what happened and that there might be other things out there, other cases labeled as hysterical that might actually be not hysterical-

Erin Allmann Updyke	Right.
Erin Welsh	Not just be because the illness satisfies some need in the patient.
Erin Allmann Updyke	No, I agree entirely. It's so rare I think to see that much self awareness and willingness to admit your own fault and how complicit you were in the suffering of another person.
Erin Welsh	Yes.
Erin Allmann Updyke	I don't think that that publicly happens in publications very often at all.
Erin Welsh	Right. And that was from 1958 which is I think just a really interesting... Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	I just think it's fascinating. And this article seemed to strike a chord with other people too. I found correspondence addressed to the British Medical Journal, which is where that one was published, about this case study. And people were like I loved this article, it was so readable, I read it before the newspaper at breakfast. And people were like oh I wonder how many other cases... Like Charcot in his hospital, there was a woman who had that but she was of course in this-
Erin Allmann Updyke	Right.
Erin Welsh	Quote unquote "insane asylum". So yeah.
Erin Allmann Updyke	I know. So many. Oh Erin, we'll talk more about it too because we absolutely still do it today.
Erin Welsh	Oh yeah.
Erin Allmann Updyke	I know.
Erin Welsh	Yeah. I'm curious to hear some of that. Yeah. And after Asher's article, after Moersch and Woltman's article, other case reports of quote unquote "stiff-man syndrome" quickly followed throughout the rest of the 1950s and into the 1960s with most authors acknowledging how long symptoms were present before diagnosis, often years, sometimes decades. And how for most people hysteria was the first diagnosis made. Or I saw one patient who was labeled as drug-seeking initially because of pain. Yep. One paper from 1960 suggested that quote "it is possible that the disorder may not be as rare as it seems. Since emotional disturbance is one of several factors which may lead to exacerbation of symptoms, these may be mistakenly regarded as of psychogenic origin." End quote. And from 1966, quote: "Frequently in medicine, when we are confronted with a new set of symptoms that we cannot explain, we readily label these as hysterical or functional." End quote.

	It feels weirdly reassuring to read that from papers back then, decades and decades ago. And even though it took a long time for change, for the tides to turn, it seems like this is beginning that a bit. The increase in awareness about stiff-man syndrome, stiff-person syndrome was not immediately followed by a better understanding of the underlying pathology of the disease and how to treat it though. In fact, the first effective treatment in symptom management was reported seven years after that Moersch and Woltman paper in 1963 with diazepam, AKA Valium. I don't know the full history of the development of diazepam/Valium but I know it first came on the market in 1963 and was primarily then used to treat anxiety but was soon prescribed by neurologists to manage muscle spasms and stiffness. And so given the high rate of hysteria diagnoses, I'm not sure if patients were given diazepam initially for anxiety or for muscle spasms, which were thought to be voluntary. Like this person is... You know what I mean? So I don't know. I didn't pick that up in any of the case reports I saw.
	But in any case, this drug remains a frontline treatment, as you mentioned, Erin. And its success in alleviating spasms gave researchers some potential clues as to the underlying disease processes in stiff-person syndrome, especially the potential role of GABA or anti-GAD antibodies. The 1970s, 1980s, and 1990s saw a steady rise in awareness of stiff-person syndrome, improved diagnostic criteria, a slightly better understanding of the pathophysiology, and some hopeful avenues for treatment including diazepam, immunoglobulin therapy, steroids. But despite this, many challenges remained for this rare disease. And to give you some idea of what I mean, I'll just read you the title of a 1977 paper. Quote: The Stiff-Man Syndrome: A Psychiatric Disease?" End quote. And I will also share a statistic from a 2002 paper which surveyed 68 individuals with stiff-person syndrome diagnosed in Germany and found that 2/3 of the 68 individuals were initially diagnosed with hysteria. So yeah.
Erin Allmann Updyke	Wow. Okay.
Erin Welsh	Yeah, that paper is from 2002.
Erin Allmann Updyke	2002. Hysteria.
Erin Welsh	Yeah. Hysteria.
Erin Allmann Updyke	As a diagnosis in 2002.
Erin Welsh	And I will say that I didn't see in the article when people were diagnosed but...
Erin Allmann Updyke	Still. Doesn't matter.
Erin Welsh	Yeah.
Erin Allmann Updyke	I mean come on.
Erin Welsh	You can give some benefit of the doubt but there's still-
Erin Allmann Updyke	A very small one.
Erin Welsh	Yeah. Yep. These misdiagnoses with hysteria or a functional neurological disorder, which you're more likely to see today in notes, aren't that surprising given that stiff-person syndrome is so often accompanied by things like phobia, anxiety, depression and just by the fact that it's a rare disorder. Because as they teach you in med school, when you hear hoof beats, you're supposed to think horses rather than zebras.

Erin Allmann Updyke	Ugh. That is that is the quote over and over and over again in med school, Erin.
Erin Welsh	Right, right. Yeah. And this delay in correct diagnosis is a characteristic shared among basically all rare disorders, most of them. And it's not the only thing they have in common, as I mentioned earlier. Limited treatment availability, challenges conducting clinical trials, inappropriate medical interventions, small research programs. And that's not even mentioning the personal and quality of life challenges that someone might experience living with a rare disorder. So even though the diseases themselves may be very different, the designation as a quote unquote "rare disease" is a useful one from an advocacy standpoint. And I want to close out this section by chatting about a couple of really impactful developments over the past few decades that have helped to put rare diseases in the spotlight.
	The first is the Orphan Drug Act. So approving a medication is not a simple thing, nor should it be. It requires pharmaceutical interest, AKA dollars, and multiple stages of trials before its efficacy and safety can be confirmed. For rare diseases, this poses a huge challenge because you need people with the disease at each of those trial phases and new individuals at each phase. And even then to show statistical significance, you often need more people than are available to participate.
Erin Allmann Updyke	Right. Think about how many thousands of people were enrolled in something like the COVID vaccine trial, right.
Erin Welsh	Right.
Erin Allmann Updyke	We need lots of people for medication research.
Erin Welsh	Yep. Yeah. It's logistically and financially challenging to say the least. And this problem drew the attention of the FDA in the late 1970s, who along with leaders of advocacy groups like Marjorie Guthrie, who I mentioned in the Huntington's disease episode, Woody Guthrie had Huntington's disease, and also Maurice Klugman, star of the show Quincy, M.E., whose brother had a rare form of cancer. All of these individuals drafted up legislation to provide financial incentives for the pharmaceutical industry to develop drugs for rare disorders. And this legislation was called the Orphan Drug Act and it was passed in 1983 and it completely revolutionized the development of therapeutics for rare disorders. For some perspective, before this act only 10 drugs for rare disorders had been approved. By 2008 that number went up to 300, translating into treatment for over 11 million people.
Erin Allmann Updyke	Wow.
Erin Welsh	It's huge. And it also kind of helps to deal with some of the logistical challenges too by like simultaneous phases. And yeah, that part I'm not as familiar with but there's lots of papers that I'll link to about that. And advancements when it comes to rare disorders, they're not just limited to drug development. The same year that the Orphan Drug Act was passed in 1983, the National Organization for Rare Disorders was established, NORD, bringing together advocates under one umbrella with a recognition that quote "alone we are rare, together we are strong." End quote. That's the NORD slogan. NORD represents more than 200 individual disease organizations and has done tremendous work in promoting and funding basic research into rare disorders, providing support and education for individuals impacted by these disorders as well as their families, and overall just raising awareness because that's one of the biggest challenges in this is just awareness. Because if you hear hoof beats, you think horses. Are you ever going to think zebras?

Erin Allmann Updyke	Right. You have to know that the zebras exist-
Erin Welsh	Right.
Erin Allmann Updyke	To even think of them in the back of your mind, right.
Erin Welsh	Right. And I would say zebras are also like a little bit more common. What about some rarer equines?
Erin Allmann Updyke	Right.
Erin Welsh	I can't think of any.
Erin Allmann Updyke	Yeah. It's not the best analogy.
Erin Welsh	Right, right. But yeah, I mean it's that sort of thing. Like you think horses, okay. You think what else? What else could it be? Zebras, donkeys.
Erin Allmann Updyke	Giraffes?
Erin Welsh	Yeah, sure.
Erin Allmann Updyke	Have hooves.
Erin Welsh	Okay. And we're talking ungulates, like that's a whole other thing.
Erin Allmann Updyke	Antelopes.
Erin Welsh	Kudu.
Erin Allmann Updyke	Okay. I don't know.
Erin Welsh	Lots of things.
Erin Allmann Updyke	But yes, I agree.
Erin Welsh	Pronghorn. Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	With the Orphan Drug Act, with NORD, there has been a lot of progress made. And things aren't perfect, right. Often medications for rare disorders are prohibitively expensive, making them inaccessible to those who need them. And some of these disorders are themselves varied. So a drug that might be effective for one person might not be for another, just like we discussed in stiff-person syndrome. But ultimately I wanted to highlight these efforts as well as sort of like that those shifts from those case reports in the 1950s where we could actually see this dawning awareness, self awareness of like oh maybe it's not hysteria. Just to appreciate how far we've come over the last 70 years, not just in terms of stiff-person syndrome and our understanding of that but awareness of all rare disorders and the challenges that they face.

Erin Allmann Updyke	Yeah.
Erin Welsh	So with that, Erin, can you tell me where we are with stiff-person syndrome today?
Erin Allmann Updyke	I would love to try right after this break.
TPWKY	(transition theme)
Erin Allmann Updyke	As with so many rare disorders and not rare disorders that we cover on this podcast, we don't have great data on the incidence and prevalence of stiff-person syndrome. But there are numbers that are cited pretty frequently. And that is that you mentioned already, Erin, the estimate is that the prevalence, the number of people living with stiff-person syndrome is I saw mostly 1-2 cases per million.
Erin Welsh	Okay.
Erin Allmann Updyke	Some might say 1-3. I will say that the Stiff-Person Research Foundation website says 4-5 cases per million. I didn't see that number other places, so I'm not sure where that estimate came from. But in any case it is an estimate because we really don't know, especially when you consider stiff-person syndrome vs stiff-person syndrome spectrum disorders, right.
Erin Welsh	Right.
Erin Allmann Updyke	But if we take that number of 1-2 cases per million and do some Erin math because it's been a while since we've done that-
Erin Welsh	It's been a while.
Erin Allmann Updyke	I know. That would be, so that people can get a sense of this, somewhere in the range of 300-600 people in the United States living with stiff-person syndrome.
Erin Welsh	Okay.
Erin Allmann Updyke	That is very rare.
Erin Welsh	It's very rare.
Erin Allmann Updyke	And between 8000-16,000 people worldwide. This is a super rare disorder. The incidence though is also estimated to be about one per million new cases every year. So we're talking about another 8000 cases worldwide every year.
Erin Welsh	Okay.

Erin Allmann Updyke	And some studies suggest that up to 65% of people living with stiff-person syndrome can no longer function independently in their activities of daily living because of a combination of their symptoms of stiffness, rigidity, pain, frequent falls, and also phobias that are related to the falls or to doing specific tasks. And I want to kind of spend a minute to talk about that, this anxieties and phobias that can result or that can be kind of what we call comorbid with stiff-person syndrome. You mentioned it, Erin, I mentioned it earlier as well. One study tried to kind of put a number on this. Like how much more common are things like anxiety, depression, or phobias in people with stiff-person syndrome compared to people without stiff-person syndrome? And they're significantly more common than in the kind of what we call general population. But overall, this one paper found that the rates were pretty similar to people living with something like MS which is another chronic neurologic condition.
	But there's a couple of things that I want to mention about the anxieties especially that can present with stiff-person syndrome. First, because stiff-person syndrome is so rare that many practitioners including experienced neurologists might have never seen a case of it before, even if they've heard of it, they might have never seen it. So it's not necessarily going to be the first thing that they think of. And because most people present to a primary care physician who's even less likely to have ever seen it before, it is very common for stiff-person syndrome to be initially misdiagnosed, just like it was called hysteria, as a primary psychiatric disorder. Like you have anxiety with these symptoms rather than you have a neurologic disease and you have anxiety as a result of it. But that isn't true in the case of stiff-person syndrome. First, the anxieties and phobias tend to be very directly related to their symptoms and very realistic and appropriate given the degree of stiffness, spasms, injuries, pain; things that can result because of the symptoms that they're having.
Erin Welsh	Right.
Erin Allmann Updyke	And it kind of goes even beyond that. This is a neurologic disorder that's affecting GABA which is a neurotransmitter that is involved in decreasing our excitatory, like decreasing that anxiety response and reducing that can further drive anxiety. And on top of that, benzodiazepines, Valium, the Valiums of the world-
Erin Welsh	Yeah.
Erin Allmann Updyke	These are medicines that function like I mentioned at that GABA receptor, they act like GABA. They are considered a first line treatment for stiff-person syndrome because they act on that mechanism. But they're also used in the treatment of anxiety disorders and they're very effective in the treatment of anxiety disorders. Especially in the past, they were used kind of like a free for all for anxiety.
Erin Welsh	Oh yeah.
Erin Allmann Updyke	Today I hope most people are using them less for primary anxiety disorders. But what that means is that somebody who has stiff-person syndrome but hasn't been diagnosed with that who gets given a benzodiazepine and has improvement of their symptoms, that might further misrepresent them as having a primary anxiety or psychiatric disorder rather than having this neurologic disorder that is stiff-person syndrome. So all of this can really, really contribute to the major delays in diagnosis that we see. One paper that I read cited an average of 6 years from onset of symptoms to diagnosis but that range was up to 18 years which is just...
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah.

Erin Welsh	Not having the big picture like the full picture of things but being like oh, this answers this. So then the other things that you may be experiencing that are not just anxiety-related symptoms, you're like oh no, well those aren't related because this is clearly treating your anxiety. So those things you're not really experiencing, it's just in your head.
Erin Allmann Updyke	Right.
Erin Welsh	Or they're not related to this. And so you're left still with like these questions of-
Erin Allmann Updyke	Right.
Erin Welsh	But is there something more?
Erin Allmann Updyke	Yeah. And I also don't want to like make this seem as though anxiety is also not real. It is, that's like a whole different situation.
Erin Welsh	Totally.
Erin Allmann Updyke	And there's neurotransmitter abnormalities involved in that as well too.
Erin Welsh	Well and it's also not just that anxiety is... I think that living with a rare disease and chronic disease on its own comes with anxiety that may not be just down to the pathophysiology of that disease. If that makes sense.
Erin Allmann Updyke	100%.
Erin Welsh	Yeah.
Erin Allmann Updyke	Absolutely. Absolutely. Absolutely. Yes. It is so much bigger than all of that. But I think it's an important kind of piece to highlight is that it is important to get the correct diagnosis. And when it comes to stiff-person syndrome and other rare disorders, it can be very difficult to get there. And so in terms of where do we go from here, I think it's really hard to say, to try and estimate like what is to come. I think there is no doubt that when a celebrity comes out as having a disorder or even bringing something like a rare disorder to the spotlight in one way or another, it really does put a type of spotlight on that disease that most other diseases don't get. So the question really now is is that going to lead to more funding? Is that going to lead to more research? Or is it not? I hope it's going to. I think that's a big hope.
Erin Welsh	Right. Or just more awareness.
Erin Allmann Updyke	Right.
Erin Welsh	Which in itself could then lead to more diagnoses-
Erin Allmann Updyke	Exactly.
Erin Welsh	And more name recognition for that.
Erin Allmann Updyke	Yeah.

Erin Welsh

Yeah.

Erin Allmann Updyke

And we might have very different epidemiology numbers in years to come-

Erin Welsh

Yeah.

Erin Allmann Updyke

Simply because of increased awareness. And I think one of the things that at least for me watching that documentary highlighted that I hope that we as a society continue getting better at when it comes to rare disorders but also when it comes to a lot of these what we call invisible illnesses and really just any things that people are dealing with is like understanding that these are all affecting people and you have no idea what it is that another person is going through when you're looking at them. And I think that that is one of the big things that for me at least that documentary really highlighted. And I think that we need to do better at in medicine and beyond medicine is recognizing that these are people, their symptoms, whether they have a name for their diagnosis or not, just believing people I think and giving grace an understanding that you don't know what another person is going through. And I think that that empathy building is very much needed in medicine and beyond medicine.

And we've highlighted and mentioned, Erin, the organizations like the National Organization for Rare Diseases that are doing a lot of this advocacy work. There's also, I want to shout out the Stiff-Person Research Foundation which does a ton of work in raising money and doing research on stiff-person to try and better understand it, to try and come up with cures. And Alison, the provider of our firsthand account for this episode, also works with a number of other people living with stiff-person syndrome who have a couple of other organizations I wanted to give a shout out to. They have an Instagram page called Bent Not Broken Autoimmune and then a YouTube channel called Stiff-Person Syndrome Heart to Heart. So if you would like to learn more about stiff-person syndrome specifically, you can absolutely check those out. And check out the National Organization for Rare Diseases as well to learn more about so many additional diseases besides stiff-person syndrome. But yeah, that is what we've got for this episode.

Erin Welsh

And we've got a lot more that if you would like to read further, there is plenty, there are plenty of sources out there. So let's go ahead and go through a few of those. I've got a whole lot. I'm going to shout out two in particular that I think are really interesting and were helpful to kind of wrap my head around this. The first is that paper by Asher called 'A Woman with a Stiff-Man Syndrome' from 1958. I do think it is a really interesting presentation of this person's experience sort of fitting this into the retrospective diagnosis and some of that self awareness. And then on the topic of rare disorders and rare diseases, there is an essay from The Lancet published in 2008 by Schieppati et al and it's titled 'Why Rare Diseases Are an Important Medical and Social Issue'. There's a whole lot more.

Erin Allmann Updyke

I have a few papers. The couple that I want to give a special shout out to are one by Hadavi et al from 2011 called 'Stiff-Person Syndrome' in The Journal of Practical Neurology. And then another that was also titled 'Stiff-Person Syndrome' from Neurologic Clinics in 2013 by Ciccotto et al. I'm almost certainly pronouncing that wrong and I apologize. I had a number of other papers as well too. There was that one that really looked at the stiff-person syndrome and psychiatric comorbidities, that was from 2021. But we'll post all of the sources from this episode and all of our episodes on our website thispodcastwillkillyou.com under the EPISODES tab.

Erin Welsh

A big thank you again to Alison for being so open and willing to chat with us and share your experience and your story. We appreciate it, the words cannot express.

Erin Allmann Updyke	Yeah. Thank you. Thank you. Thank you. Thank you also to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Welsh	Thank you to Tom Breyfogle and Lianna Squillace for the amazing audio mixing.
Erin Allmann Updyke	Thank you to everyone at Exactly Right network.
Erin Welsh	And thank you to you, listeners. We hoped that you learned something from this episode.
Erin Allmann Updyke	And a special shout out as always to our patrons. Your support means the world to us. Thank you so, so, so, so much.
Erin Welsh	Truly, truly. Well until next time, wash your hands.
Erin Allmann Updyke	You filthy animals.