Seizing Life, episode 139
The NORSE Institute:
A Mother's Loss Drives Awareness and Research into a Devastating Form of Epilepsy
Guest: Nora Wong
(Transcript)

Kelly Cervantes: Hi, I'm Kelly Cervantes, and this is Seizing Life, a monthly podcast produced by CURE Epilepsy. This month on Seizing Life, I'm happy to welcome Nora Wong to the podcast to talk about a rare and devastating form of epilepsy called NORSE. As founder and executive director of the NORSE Institute, Nora works to increase awareness of NORSE, foster community among families and doctors touched by this sudden and severe epilepsy, and build a collaborative environment for researchers to learn more about NORSE.

Nora, thank you so much for joining us today. To start off, I would love to get an idea, general definition around what NORSE and FIRES entail, what they are.

Nora Wong: Sure. Well, thanks for having me, Kelly. So NORSE is an acronym for a presentation, not a clinical diagnosis. It's a presentation of new-onset refractory status epilepticus. So maybe I should begin by saying status epilepticus is a medical emergency. It's a prolonged or cascade of seizures that usually lasts for five minutes or more, and it's associated with high morbidity and mortality. And people arrive at status from a number of things. It can be caused by stroke, traumatic brain injury, the withdrawal of alcohol or the abuse of alcohol, drugs, near drowning.

So a number of things could cause status epilepticus. And if after at least two or more appropriate drugs are applied and it continues, then it's known as refractory status epilepticus. So NORSE is new-onset refractory status epilepticus. So basically it's seizures that arrive out of the blue, that don't respond to treatment, that primarily affects young adults and children who are healthy with no history of epilepsy. In about 50% of the cases, there's no biomarker. Despite extensive testing, they find absolutely no cause.

So it's a traumatic experience for both the doctors, as well as the families because it's something that just arrives. These people land in the emergency. They were formerly very healthy, just walking around, and some of them have a preceding fever. So if a fever precedes the seizures by two weeks to 24 hours, then those cases are considered febrile infection-related epilepsy syndrome. So FIRES is a subset of NORSE. It's the fever that is the distinguishing characteristic.

Kelly Cervantes: So just generally terrifying and traumatic for everyone involved, I'm sure. In 2015, you founded the NORSE Institute to try and gather the professionals who could help learn more about NORSE, and this was after the loss of your son, Daniel. Can you share with us, tell us a little bit about Daniel, who he was, and also about his tragedy with NORSE?

Nora Wong: Sure. Daniel was 22. He had just graduated from Stanford. On Father's Day 2013, he started work as a financial analyst, because he majored in economics and public policy. He was incredibly smart, but also very kind. He had an unusual memory. He also had some sensory integration deficits, and so that made him very, very empathetic towards other people who were a little different, or as he put it, hey yo jacked up by life. So he worked for an investment firm that focused on creating investments for nonprofits.

As I said, he graduated June 2013. And three months later, his roommate found him unresponsive, half-dressed, and sent him to the local hospital, one affiliated with Harvard Medical School. And he started seizing then and he never regained consciousness for 79 days. He started seizing and no one knew why he was seizing. So that is the familiar trajectory of NORSE, that a perfectly normal, healthy person who was going about their business might have felt a little ill because there's often a prodrome of flu, some kind of stomach bug, which he had.

He had a fever. He thought he had a stomach bug and he was getting better. Now, that's also important. So he had a fever, he was getting better, and then he started seizing and they couldn't stop the seizures. There was every test, every medical test, the initial MRIs, CAT scans, they all came back with no results. Everything was normal, and yet they couldn't stop the seizures. And the amount of medication that he required to even start to control them was very unusual. It's very high dosages.

Eventually his other organs started failing. And so at the end of 79 days, his doctors thought he would not survive, and they asked us to stop treatment. And that is another common occurrence in NORSE that often is not spoken about, and that the morbidity and mortality is so significant that life expectancy and quality of life is presumed to be very poor. That cessation of aggressive treatment is one of the reasons that the patients die.

Kelly Cervantes: Which is a challenge to overcome it in itself for a condition that is so poorly understood. This is a family, these are families that are likely very unfamiliar with the medical system. You're not talking about seasoned advocates who have been in and out of the medical system and have learned how to fight for what they need. So that adds a whole other element to this as well, I imagine.

Nora Wong: Yes, exactly. And it is not only the families that are under enormous pressure, but the doctors also because this is a totally new space. As I mentioned earlier, that status epileptic is usually is caused by something. So you treat the status epilepticus according to the underlying cause. So if someone arrives and they've been hit on the football field and they've had a huge concussion, or someone's been in a car accident and they're bleeding, then you treat the cause, the obvious cause.

But in these cases, for about 50%, there's no cause. So the treatment is still being determined. And then the other important thing is that the language with which to communicate what's happening is also just being developed, because we were told repeatedly when we asked, "Well, what's wrong?" And they would say, "Well, we don't know. He has seizures." And that's the only thing we were told. But as a result, his kidney stopped working. He had heart problems. He developed blood clots.

There was multi-organ failure, but we didn't understand why because we were told everything came back negative. He just had seizures. And the doctors in the meantime, because I've worked with them, they are frantically doing every relevant test. And in my son's case, they did extensive testing and then they thought, "Well, maybe we did them too early. Maybe he hasn't developed antibodies to whatever we're testing." And so they did them all again. Nothing.

Brandon: Hi, this is Brandon from CURE Epilepsy. Do you have questions about seizures, medications, treatments, or other areas of epilepsy? CURE Epilepsy's new video series, Epilepsy Explained, provides answers to help you better understand the basics of epilepsy. Each month, a different expert offers short, easily understandable answers to questions from our community about a particular area of epilepsy.

Doctors and researchers who are leaders in their field will cover questions about seizures, diagnosing epilepsy, medications, surgery, and many more topics. New episodes of Epilepsy Explained will be available on CURE Epilepsy's website and YouTube channel on the third Wednesday of every month. Now back to Seizing Life.

Kelly Cervantes: So with all of this lack of information, Nora, I wonder how did you discover that NORSE was the cause and when did you first hear of NORSE?

Nora Wong: No one actually said the word to me. We were in the ICU for all that time. So we were there for 79 days, which is unusual. Most people cycle in and out of the ICU within a week. And one of the early doctors who cycled back saw us and she said, "Oh, you're still here?" And so she was so surprised. And so she went to the computers by the nurses' desks, came back and said, "I think he has this. Do you want to see it?" It was an article. It was a printout. And she just said, "And so when he wakes up, the question will be what his function is."

And she walked out of the room and she never came back. I read the article and it was a study on patients with refractory status epilepticus new-onset, and they used the word NORSE. And all the patients either died or had brain damage. And I thought, this can't be my son. There's just no way. This is not going to happen. This can't be. No one ever told me this. And then when he wasn't getting better, because the article pointed out how these were perfectly healthy people and nothing was working and the outcome was very poor.

And then I didn't show anyone, didn't say anything for a while. I thought, you know what? This is starting to feel very familiar. So I asked one of the doctors, is this NORSE? And the doctor didn't answer me. I don't think that he was trying to mislead me. I think he had not heard of the term. It's a very new term. Actually there are many terms. There had been many terms for this rare presentation.

And then I just said, "Well, does he have status epilepticus?" Because in the preface of this article was saying how dangerous status epilepticus was, and he just said yes.

And at that point I just stopped asking, and I never asked again because there was another doctor who told us there is no reason to believe that he will not regain full function when he wakes up. So those are the two times I'd heard the word function and I chose to believe the second one. So I thought, he doesn't have NORSE. He's going to be fine. And it wasn't until really around the 78th day, 77th, 78th day that his doctors told us that they didn't think he would survive. And if he did, he would have no capacity for new memory, not have his former memories, probably not be able to move.

But until that time we thought, I thought he was going to wake up and I was going to feed him a good meal, take him home, get him fat again, and then he'd go to work. I had no idea that this was the expected prognosis.

Kelly Cervantes: So after Daniel's passing, you started to do some more research. You eventually determined that NORSE was the cause, and you founded the NORSE Institute with several doctors. Can you tell us about the primary goals of the NORSE Institute and how you came to found that?

Nora Wong: Well, it was by my bugging people to find other patients, to start a registry, to start a study. Because at that point I didn't know what he had. I presumed that it was NORSE because it followed that trajectory of that article, but I didn't know. No one told me that. And it wasn't until one of his doctors said, "Oh, well, there are two doctors at Yale, Larry Hirsch and Nicolas Gaspard, who are thinking of studying refractory status epilepticus, of which NORSE is a subset. So you might be interested in their study because it would include patients like Daniel."

And this was almost a year after Daniel died and I thought, oh, so you're telling me now what he died of? And so I wrote back to Nicolas Gaspard, he was in Brussels that point, and Larry Hirsch and Emily Gilmore met with me at Yale. Nicolas was on Skype from Brussels, and we started to talk about NORSE. And they were very open to hearing our experience, despite never having Daniel as a patient. They wanted to learn more.

And I wanted to find out more about their study, which is refractory status epilepticus, which includes all the other people who might have stroke, traumatic brain injury, so on. It was a very large study. They had no money for the study. And given their interest and the only possibility of learning more about NORSE, my husband and I decided that we would fund their study if it would focus on NORSE. So that was the beginning of the first multicenter study of NORSE.

It was an observational study. And our Skype calls then drew more and more people and they became my medical advisory board. And I formed the NORSE Institute basically with Nicolas Gaspard, Larry Hirsch, and it was very doctor heavy because only the clinicians were using this term. And then the other complication is that there were many different terms being used. Some people refer to it as NORSE.

The people in the pediatric world were referring to it as FIRES, because many of the children who have this presentation have the fever first. And then other people decided they want to use other words, de novo status epilepticus, super-refractory status epilepticus. There are many different terms. So as a result, everyone was off in their own direction doing their own research. So I said to Larry and Nicolas, "Would you decide what to call it?" So common sense.

And that's what they did. They did it on their own, and it took almost a year to decide within our small group. He took it out to other experts abroad. And then the consensus definitions of NORSE and FIRES were presented in the first international conference on NORSE and FIRES in Salzburg, and then they were published in 2018.

Kelly Cervantes: That's incredible. I don't think people understand when you are working with these new symptoms or conditions or even diagnoses that you have to get the language first. You have to establish what the language is, what it constitutes, and that is the very first step that happens. There can't be names for some of these things.

And then once you have a name, then you can compile the data from all of the different places using all of the different names that were once out there. And I understand that that was one of the first initiatives that the NORSE Institute worked on was just building a data registry, collecting that data from families so that it could then be analyzed. Tell us about that and why that was so important.

Nora Wong: Sure. So once the consensus definitions were out there, then people were discovering that there might have more and more cases. So we wanted to capture that information, and plus, we want to draw people together. So we have a website, norseinstitute.org, and it has information for both the professionals as well as the families. And on the website there's a portal to the NORSE Family Registry.

It's important to draw information from the families about demographics, the time of onset, and what the treatments were for all the patients and the outcomes post-discharge if the patient survives. So the registry is there and it's a very open and collaborative project. And there is also now a biorepository, a NORSE/FIRES open and collaborative biorepository at Yale.

And that is unusual in that it has an IRB or has ethics approval to accept bios samples from anywhere in the world using their IRB or permission so that the donating center doesn't need to file their own IRB, which can take a year. And they can send samples to NORSE, this biorepository at Yale. We not only house the samples, but we do basic analysis. But we make the information public. We don't hold onto the information.

So that information has been sent to CHOMP and UCSF and remaining samples at the biorepository are not simply kept at Yale. Investigators from all over the world can apply for those samples. And if those investigators have a good research design and they have funding to analyze the information further, we send those samples out. So we have sent samples out to basic scientists to look at...

They might want to look at it from one perspective. Another person wants to look at cytokine analysis. Another person wants just to do analysis on the blood. We want to encourage analysis from every single perspective because it's just a given that people have no idea what this is.

Kelly Cervantes: Well, and then obviously having all of this data available hopefully excites more scientists to then study NORSE. I wonder with the available information and data sets that are out there, what are the current treatments for NORSE that are recommended?

Nora Wong: Well, we do have a treatment protocol on our website, so it's the norseinstitute.org website. And in general, I think that there's evidence to point to NORSE being immune modulated. So they assume that there's some dysfunction in the immune system. And so they have been using immunotherapy, which is basically therapy to modulate the immune response. The evidence has been that there's just inflammation and an increased level of cytokines, which are proteins in the body that affect the immune system.

So when you ask about what types of medications, it's often steroids or specifically the second line treatment would be anakinra, tocilizumab, rituximab, and intrathecal dexamethasone. And they also use the ketogenic diet. Now, it's like I'm throwing these terms out. Again, people don't know why many of the patients present with these symptoms. And the assumption is that the actual underlying cause could be many different reasons.

So there have been cases written up and sometimes televised of a patient having NORSE receiving anakinra and miraculously going back to college and Division 1 sports. And that is true, but at the same time, there are patients who have received anakinra and they've died. So that is the complexity and the challenge of NORSE that the immune therapies that I've just mentioned might work for one person, but not for another.

Kelly Cervantes: Not unlike generalized epilepsy where it's a spectrum disorder and there could be a wide variety of causes. It sounds like NORSE is similar in that regard where unless you know what the cause is, it's going to be really difficult to treat it. And as you mentioned, 50% of patients, they're not able to determine what that cause is, which I'm sure makes treating it just that much more challenging.

Nora Wong: Yes, there is something that families should know about though, especially those who have a loved one in the acute phase. If they wish to donate samples to the biorepository and they are in the active phase and they wish for this information, the biorepository usually deidentifies all the information and just looks for general trends.

But if requested and the patient is in the active phase, they will send back cytokine results. They will rush them back because sometimes the cytokine results may guide or influence the treatment, like which immune therapy to use. Sometimes it doesn't, but sometimes it does. So there is that option if families choose it.

Kelly Cervantes: That's incredible for families to know about and the doctors to know about too so that they can suggest it. What other exciting research is going on with NORSE right now?

Nora Wong: Well, we've issued several grants through AES, as well as through CURE. One of our current ones is the Rare Epilepsy Partnership Award between CURE and the NORSE Institute, and it was awarded to Vincent Navarro in Paris. So this is an international collaboration, and they will be looking at pathways that influence drug resistant epilepsy in the survivors of NORSE. Because as I mentioned, the people who do survive, many of them do have refractory seizures and develop epilepsy.

And just as people don't know what to do many times in the acute phase, well, if you think of it, even though it has a very high mortality rate, the majority of the patients survive and long-term outcomes is like unexplored territory. And so many of the professionals on my board, they are now looking into long-term outcomes and what are they, and of the types of epilepsy, how can they be treated so that CURE, Rare Epilepsy Partnership will address one of those issues on drug resistant epilepsy.

Kelly Cervantes: I know that CURE Epilepsy is very excited to be working with the NORSE Institute on that grant. You mentioned that families can send out samples to work with the NORSE Institute if they are in that acute phase. What else should families know? What other services or resources are available to them through the Norse Institute or elsewhere?

Nora Wong: Well, they can find all of them on our website, but we have regular meetings. There are a number of meetings. Every year since around 2018, 2019, we've had NORSE round table meetings at American Epilepsy Society, and those are primarily for professionals just to talk about their research and not actually to get to know each other because again, it's a rare disorder. Some of them have been hybrid, so on Zoom, and families can attend.

We also have our annual Scientific Symposium and Family Conference, which are virtual, and families are invited to the Scientific Symposium. And usually there is one family member who addresses the scientists and clinicians at the Scientific Symposium just to drive home, this is what you're working for. This is the people you're working for. And then we have Family Conference in which clinicians and scientists attend or speak, but families also participate. And there are breakout sessions there for all the different groups.

We have the bereaved, we have survivors, and we have caregivers and the scientists and clinicians. So they have been very important platforms for people to communicate. And we have NORSE family meetings, and they're just going to go monthly as of July. And we have them during the day and at night because we have people in the Far East and in Australia. NORSE occurs all over the world. And it's just very comforting to know that there's someone else in the universe who has gone through something similar, never exactly the same, but something similar. It's important.

Kelly Cervantes: It's so important to have community and people who understand where the grief is not shoved down or made to hide in the shadows and the reality of the situation can be held in its perfectly honest truth. Nora, you have done so much in such a short period of time with the NORSE Institute. It's really remarkable and impressive.

You are a force, and I am just utterly impressed by you and all you have done. Sending so much love and strength your way as we remember Daniel and all of the work that you are doing in his honor. Thank you so much for being with us today and sharing your experience and wishing you all the best.

Nora Wong: Thank you, Kelly. Thank you for having me.

Kelly Cervantes: Thank you, Nora, for all the work you've done and continue to do with the NORSE Institute to raise awareness, improve knowledge, and support research into NORSE. Like the group of mothers who founded CURE Epilepsy 26 years ago, Nora exemplifies the power of parents in advocating for epilepsy research.

CURE Epilepsy is dedicated to funding initiatives and research that will improve our understanding of this devastating condition, develop new therapies, and ultimately lead to cures for epilepsy. If you would like to help us achieve our goal of a world without epilepsy, please visit cureepilepsy.org/donate. Thank you.

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