Seizing Life, episode 94
Inflammation's Role in Epilepsy and How it Might be Prevented
Guest: Dr. Nicholas Varvel
(Transcript)

Kelly Cervantes:	00:00	Hi, I'm Kelly Cervantes and this is Seizing Life, a biweekly podcast produced by CURE Epilepsy. Today, I'm happy to welcome Dr. Nicholas Varvel to the podcast. Dr. Varvel is an assistant professor in the Pharmacology Department at Emory University. He is also an epilepsy researcher and a 2019 CURE Epilepsy grant recipient. He is here today to talk about the connection between acquired epilepsy and inflammation and how discoveries made through his research could lead to new treatments for preventing the onset of seizures. Dr Varvel, thank you so much for joining us today. To kick off the conversation, can you start by explaining the different ways that people might develop epilepsy, specifically the difference between acquired and genetic epilepsy?
Dr. Nicholas Varvel:	01:03	So thank you for hosting me on your podcast today. It's a great pleasure to be able to share my research with your viewing audience. So epilepsy is a disease that affects about 1 to 2% of the population. We largely group them in two categories. So the first are what will we call the genetic epilepsies. So these are caused by mutations in one's genomic material that are either inherited or that perhaps can occur spontaneously in one individual. We call these de novo mutations.
Dr. Nicholas Varvel:	01:38	The second class of epilepsies, and in fact, this is the class that we are interested in, are what are called the acquired epilepsies. These are epilepsies that are caused by physically traumatic event in one's life. So risk factors for the development of the acquired epilepsies include stroke or bleeding into the brain, brain infections or brain tumors, seizures that are caused by a high fever that we call febrile seizures and other occurrences of prolonged seizure activity that we clinically define and call status epilepticus.
Dr. Nicholas Varvel:	02:16	So the immediate consequences of status epilepticus include damage to the brain and activation of the body's immune system. Long term consequence of status epilepticus is the development of epilepsy or what we call epileptogenesis, wherein the brain converts from normal to one of epilepsy. This is the process that we are interested in in stopping.
Kelly Cervantes:	02:43	Amazing. I want to get to epileptogenesis in just a minute, but I also understand that there is a bit of overlap in between the genetic and the acquired epilepsies. Can you talk about that a little bit?

Dr. Nicholas Varvel:	02:58	Sure. So clinically, unprovoked seizures are one of the defining features of both genetic and acquired epilepsies. The areas of the brain affected are also similar between the two. Unfortunately, individuals that suffer from either epilepsies experience behavioral comorbidities, such as depression, anxiety and cognitive decline, which may be even more debilitating than the actual seizures themselves. These comorbidities can erode one's quality of life and negatively impact loved ones and caregivers.
Kelly Cervantes:	03:40	So, correct me if I'm wrong here, there's an overlap certainly in the systems and the cause and effects, which you pointed out. But there is also some belief that perhaps some people who have acquired epilepsy may have genetics that make them more predisposed. Am I getting that right?
Dr. Nicholas Varvel:	04:04	Yes. There is a growing recognition that genetics plays a prominent role, if not a major role, in the development of the acquired epilepsies. However, it should be it's more of you have a genetic predisposition for the risk of developing the acquired epilepsies. It's unlikely to be one gene. It's probably a collection of genes that elevate one's risk.
Kelly Cervantes:	04:33	Got it. Now, I want to get back to epileptogenesis, which you brought up earlier, which is the development of epilepsy in a brain. What is actually happening during epileptogenesis?
Dr. Nicholas Varvel:	04:46	So this is a process that we need to learn a lot more about. Clearly, cell death and a robust inflammatory response is involved, but there are also changes to a very specialized structure in the brain that is called the blood-brain barrier. In healthy individuals, the blood-brain barrier acts as a selective barrier between the body and the brain. By selective, I mean that it only allows certain molecules and perhaps even immune cells into the brain, but after seizures, the blood-brain barrier can become eroded. This selective permeability is eroded and then allows many more cells as well as peripheral molecules to enter into the brain.
Kelly Cervantes:	05:38	How long can that take before someone's brain injury or whatever the instigating factor is, how long does that process take before they could potentially develop epilepsy?
Dr. Nicholas Varvel:	05:50	So this is a very good question. The answer is that it's quite variable. In fact, it can take anywhere from a few months to many, many years. The current data indicate that for every five people that experience the prolonged seizures of status epilepticus, about two of them will develop epilepsy over the

		next 10 years. So you can see that this is a very long and drawn out process by which person can develop epilepsy after a traumatic brain injury.
Kelly Cervantes:	06:20	I mean the 10 years is quite a long time to be able to correlate that back to that particular injury.
Brandon:	06:30	Hi, this is Brandon from CURE Epilepsy. Since 1998, CURE Epilepsy has raised over $85 million to fund more than 270 epilepsy research projects in 17 countries. Learn what you can do to support epilepsy research by going to cureepilepsy.org. Now back to Seizing Life.
Kelly Cervantes:	06:50	Now, I understand that you were not initially working in epilepsy research. What brought you into this particular field?
Dr. Nicholas Varvel:	07:01	So, yeah. That's a great question. My initial training, scientific training was in Alzheimer's disease. Alzheimer's is a disease, it's a chronic disease that also involves a very robust inflammatory response, but this is drawn out over again many, many years, probably even longer than the epileptogenic process. So in my initial postdoc, I had the liberty to sort of follow my intellectual inquiries. I began to look at more acute injury models such as the seizure models.
Dr. Nicholas Varvel:	07:41	I made what I thought was the very fascinating discovery that after seizures, there is a very specialized immune cell called a monocyte that enters the brain. So I began to ask questions of, "Well, what is the consequence? What could these monocytes be doing in the epileptogenic process? Are they providing a beneficial role or perhaps are they providing a negative or a bad role?"
Kelly Cervantes:	08:08	I want to dive into monocytes here in just a minute. But what do we know about the connection between inflammation and epileptogenesis and the onset of seizures?
Dr. Nicholas Varvel:	08:19	So we know that these events are linked in some way, but we don't exactly know how. It is our idea, or at least in science, we call this our hypothesis, that the inflammation might be playing a causative role in the development of the acquired epilepsies and perhaps even the debilitating comorbidities that are associated with the disease.
Kelly Cervantes:	08:44	Okay. How do you specifically target these inflammatory response, these monocytes?

Dr. Nicholas Varvel:	08:55	So my colleagues and I have been interested in selective targeting of the inflammatory response after seizures for many years. We are trying to inhibit this inflammation by using small molecules or drugs. One of the approaches that we've taken is targeting what is called prostaglandin signaling. So prostaglandins are inflammatory molecules that are involved in the activation of specific pathways after injury, as well and specifically after the seizures. My CURE grant has focused on the selective targeting of the inflammatory cells called monocytes, which are normally in the blood, but then enter the brain after seizures.
Kelly Cervantes:	09:42	Monocytes are good, they're bad, they are not supposed to be in the brain? What is their purpose?
Dr. Nicholas Varvel:	09:49	So typically in the normal brain, you don't see many, many monocytes at all. In fact, it's largely devoid of the cells. But after seizures, my work has demonstrated that a number, a very large number of monocytes enter the brain, specifically the hippocampus, after the prolonged seizures of status epilepticus. But these monocytes don't seem to be going in right away. In fact, that there seems to be this delayed response. In fact, they're coming in about 24 hours after. So this opens up an opportunity to target the cells with small molecules.
Kelly Cervantes:	10:30	So we don't want the monocytes there. Do you know what the monocytes are doing in the brain?
Dr. Nicholas Varvel:	10:36	We don't exactly know what they're doing, but we do know that if we keep them out, at least in the short term, we have less neuronal damage, there's less inflammation, and there is a less erosion to the blood-brain barrier. We're currently asking questions, if we keep them out, do the animals develop epilepsy and then does it also relieve the cognitive comorbidities that are associated with epilepsy?
Kelly Cervantes:	11:03	Oh, that's fascinating. So if you can get in there right after this seizure before the monocytes flood the brain, then potentially you can prevent the patient from developing epilepsy from those who have the potential to develop an acquired epilepsy. But you also have the opportunity for those who maybe have a genetic epilepsy from having them develop these comorbidities. So this research could really have a huge impact in the entire epilepsy patient population.
Dr. Nicholas Varvel:	11:38	That's correct. This is indeed our hope.

Kelly Cervantes:	11:43	Of course, I love that you mentioned your CURe grant that you received. This science is just such a perfect example of CURE's patient focused research mission. How has the CURE Epilepsy grant helped you in your research and with your career?
Dr. Nicholas Varvel:	12:04	So I was fortunate enough to receive my grant from CURE Epilepsy to investigate the role of monocytes at a very important time in my career. So as a young investigator starting up my lab, it's important to receive funding from organizations such as CURE that are willing to give a chance to young investigators with perhaps new and novel ideas. I'm happy to report that I used a lot of the data that I generated using the CURE grant actually allowed me to receive a much larger grant from the NIH to further promote, build my lab and investigate the role of inflammation in epilepsy.
Kelly Cervantes:	12:47	So congratulations on the NIH grant. That is incredible news. So excited to hear that your research is going to continue moving forward. What are your goals for your research in the future?
Dr. Nicholas Varvel:	13:04	So my colleagues and I are also working very hard to develop drugs to selectively target the inflammatory response, both in prostaglandin signaling, as well as stopping monocyte entry into the brain. This is of course a very long and tedious process to get it right. It requires time and demonstration that our drugs are safe and effective in our rodent models of the disease before we can safely test them in humans. But our hope is that we will be able to move into human clinical trials hopefully within the next five years.
Dr. Nicholas Varvel:	13:43	I think it's also important to point out that a lot of the information that we are able to acquire in our current work in epilepsy could also be applied to other disease, other brain diseases that involve an inflammatory response mainly specifically involving monocyte entry into the brain. So it's possible that the information that we glean can be very comprehensive.
Kelly Cervantes:	14:12	Well, we are very excited to see where your research heads. I know CURE Epilepsy is just so honored to have helped fund you on this journey. I know we'll be waiting with bated breath to see how those clinical trials go and hopefully have a new drug on the market. Dr. Varvel, thank you so, so much for joining us today. The research that you're doing is so important to this community. We are so fortunate to have you as an epilepsy researcher. Thank you so, so very much.

Dr. Nicholas Varvel:	14:47	Thank you for having me today. It was a pleasure speaking with you. Again, thanks to CURE Epilepsy, and importantly, thank you to the donors of CURE Epilepsy that allowed me to perform my research.
Kelly Cervantes:	15:02	Thank you, Dr. Varvel for helping us understand acquired epilepsy and the role that inflammation plays in the development of seizures. Thank you for the work that you and your colleagues are doing to help find new treatments to prevent the onset of epilepsy. For more than 20 years, CURE Epilepsy has understood the importance of basic research like Dr. Varvel's in paving the way for new epilepsy therapies. We hope you will help us in our continued support of young researchers with innovative ideas who are working to find a cure for epilepsy. Please visit cureepilepsy.org/donate. Through research, there is hope. Thank you.
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