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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Discussing Dravet Syndrome: Diagnosis & Treatment

Announcer:
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Your host is Dr. Jennifer Caudle and will be joined by Dr. Elaine Wirrell. Here's Dr. Caudle now.

Dr. Caudle:
Dravet syndrome is a severe form of epilepsy that begins in infancy and has lasting impacts on a patient throughout their entire life. Because of this, it's essential that we stay up to date on the latest diagnostic and management strategies; and who better to walk us through these essential strategies than a world-renowned speaker on Dravet Syndrome, who we'll be hearing from today.

Welcome to *NeuroFrontiers* on ReachMD. I'm your host, Dr. Jennifer Caudle, and joining me today is Dr. Elaine Wirrell. She serves as both the Director of Pediatric Epilepsy, as well as the Director of the Child and Adolescent Neurology Residency Training Program at Mayo Clinic. Dr. Wirrell, welcome to the program.

Dr. Wirrell:
Thank you very much for inviting me.

Dr. Caudle:
Well, we're excited that you're here. So, why don't we start, Dr. Wirrell, by doing some level-setting for our audience. Can you tell us more about what Dravet Syndrome is and what causes it?

Dr. Wirrell:
Sure. So, Dravet Syndrome is a relatively rare form of childhood epilepsy, but it's not as rare as some people think. There was a study, actually, in California that looked at all of the patients in the Kaiser Permanente Region and found that it was about 1 in 16,000 children, so rare, but not so rare. And it is an epilepsy that is quite severe; it starts in the first, typically, 20 months, often in the first year of life. The children, generally, are developmentally normal before the seizures start, and then the seizures start, and the seizures are drug-resistant, meaning that they don't respond well to the usual anti-seizure medicines. It is a syndrome that is life-long, so these patients suffer from life-long epilepsy. I had mentioned they're developmentally normal, initially, but, , over time, typically by the late pre-school years, we see that the children are not gaining the level of development that you would expect and so by adolescence and adulthood, essentially all of them have variable degrees of intellectual disability. And then there's other problems that can go along with that, as well, but predominantly, it's very challenging seizures, and in early life recurrent episodes of status epilepticus. As far as what causes it, it is a genetic epilepsy. It's due to a pathogenic variant in a gene called the SCN1A gene, and it's important that there are other genetic changes in that SCN1A gene, and normally some of them actually lead to Dravet Syndrome. There are more severe, mutations that lead to Dravet; the less severe ones can lead to a type of epilepsy called genetic epilepsy with febrile seizures plus. But if we look at kids with Dravet Syndrome, more than 80% of those children will be found to have a more severe pathogenic variant in the SCN1A gene.

Dr. Caudle:
And what signs and symptoms make you suspicious of the possibility of Dravet Syndrome in a child?

Dr. Wirrell:
So, it's a pretty characteristic presentation and I think as a child neurologist, it's really important that we recognize that. And so typically, as I had said, it's a child who previously is neurologically and developmentally normal and the seizures almost always start in the first

year of life, occasionally up to 20 months, but most of them in the first year. And the typical presentation is a prolonged seizure that occurs with fever, oftentimes it's a prolong hemi-convulsive seizure, meaning that it affects one side of the body. And then over time, what we see is those seizures recur and so one of the very characteristic features is that they switch sides, so you might have a prolonged right-sided hemi-convulsive seizure at five months and then at seven months, you have it now affecting on the left side. And fever and hyperthermia are very, very strong triggers for the seizures, so some of these kids, after they get their vaccinations and develop fevers as a result of that, it's not caused by the vaccine, but it's triggered by the fever that is a reaction to vaccine, or children who have some type of viral illness and have a fever, or sometimes even children that are in a warm environment or put into a warm bath, that can be a trigger for the seizures.

Dr. Caudle:
Interesting. So, once you notice these symptoms, Dr. Wirrell, what diagnostic tools and best practices do you use to confirm your suspicions?

Dr. Wirrell:
So, the way that we make the diagnosis is with genetic testing. Most of these children, if we look at their imaging studies or their EEGs, those are not, terribly helpful. The MRI studies are typically normal, the EEGs may show some discharges, but again, it's not specific, they can show some generalized discharges or focal discharges or sometimes just slowing after a seizure, or sometimes they can be normal. So what we do is we look for a pathogenic, variant in the SCN1A gene, and that is done in most cases now with an epilepsy gene panel. You can do a specific test looking at SCN1A, in particular, but now most people are really doing those genetic panels.

Dr. Caudle:
OK. Excellent. For those of you who are just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm your host, Dr. Jennifer Caudle and I'm speaking with Dr. Elaine Wirrell about Dravet Syndrome. So, Dr. Wirrell, we were just speaking about diagnostic strategies for Dravet Syndrome, but now, let's shift our focus and talk about treatment options. So, what does the treatment landscape look like?

Dr. Wirrell:
So, the treatment landscape is actually changing as we speak and it's actually a very exciting time for clinicians and also for families whose loved ones have Dravet because we've seen a lot of advances in this field. Just a couple of years ago, we looked at, you know, what should be the first treatments and, typically, traditionally what's been the first treatments are a combination of either Clobazam or Valproic Acid. But we know that even with that combination, still more than 50% of children do not really get a significant reduction in their seizures, and so continue to have fairly frequent seizures despite that. There have now been three recently approved medication, by the FDA; Epidiolex, Stiripentol, and most recently Fenfluramine. So those have all, I think, changed the treatment landscape.

Dr. Caudle:
OK. And what are some promising research areas? Are there any potential treatments in the pipeline that you're excited about?

Dr. Wirrell:
There are. Because we know the gene and we know what this gene does, there's now a couple of therapies that are being looked at; one of them in clinical trials. And the clinical trial is something called the anti-sense oligonucleotide, and that really targets, the SCN1A and it increases the amount of protein production, so it corrects the haploid's efficiency of the SCN1A protein and restores normal protein levels. That has been shown, actually, in animal models to be effective and importantly, also reduces the mortality risk because in the clinical model as well as in animal models, we see fairly high mortality and in animal models, the treatment with the anti-sense oligonucleotide actually rescued that mortality, so that's very exciting. Currently that agent is in clinical trial, so we'll see how well it works in children.

Dr. Caudle:
Excellent. And finally, Dr. Wirrell, since a patient with Dravet Syndrome is cared for by a multi-disciplinary team, what are some strategies the team can use to improve patient care?

Dr. Wirrell:
Yeah, so I think when we focus on children with Dravet Syndrome, and this really goes to all children with early-onset drug resistant epilepsy, I think we really need to focus on the whole child. So, certainly seizures are very, very important and we spend a lot of effort on trying to reduce seizures, but we also want to be sure that we are focusing on not over-treating that child, and so trying to avoid unnecessary polypharmacy; all of our anti-seizure medicines have potential for side effects, so we really want to choose the medicines that are working best and in children with Dravet Syndrome, most of them need to be on more than one medication, but we want to minimize excessive numbers of medication and excessive side effects. The other thing that's really important is to focus on some of the non-seizure symptoms of Dravet Syndrome, and those are things like cognitive delays, behavior problems over time, many of these

children develop gait disorders, so they kind of have a bit of a crouched gait, and then sleep disorders. And so really having a multi-disciplinary team who can address those issues as well and make sure that the child is really set up to succeed at school. This is obviously a big concern for families, a very life-changing diagnosis for families and so family support and, particularly, sibling support is really important and so involving social work and there's also great organizations, there's something called the Dravet Syndrome Foundation that is very, very supportive to to families who are receiving this diagnosis and also a really good place for families to stay in touch, to know, sort of what are the up and coming treatments for that.

Dr. Caudle:
Excellent. Well, those are some very helpful strategies for us to think on and implement as we come to the end of today's program. I'd like to thank my guest, Dr. Elaine Wirrell, for joining me to discuss Dravet Syndrome. Dr. Wirrell, it was great having you on the program.

Dr. Wirrell:
Thank you very much. It was a pleasure to be there.

Announcer:
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