R.C.P.U. NEWSLETTER

R.C. Philips Research and Education Unit

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Dravet Syndrome

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Introduction

Dravet Syndrome (DS), first described as severe myoclonic epilepsy of infancy (SMEI) by Charlotte Dravet in 1978, is a rare early childhood genetic syndrome characterized by the onset of seizures within the first year of life after initial normal development. It is one of eight epileptic encephalopathy syndromes, which present with progressive behavioral and cognitive decline after the first episode of seizure-like activity. DS is on the more severe spectrum of childhood epilepsy syndromes and is associated with intractable epilepsy and progressive neurodevelopmental delays that persist into adulthood.

Dravet Syndrome affects one in 40,000 children, and affects males and females equally. The most common cause of DS is a *de novo* mutation in voltage-gated sodium channel gene *SCN1A*.

Clinical Features

Seizures

Seizure onset is generally within the first year of life. These initial seizures are often associated with fever, but in general patients with Dravet Syndrome are sensitive to increases in temperature such as warm baths and warm weather. Seizures are pleomorphic and can range from simple febrile seizures to intractable epilepsy. Affected individuals usually present initially with generalized tonic, clonic, and tonic-clonic seizures. Often these are unilateral and alternate between left and right. Later, other seizure types can manifest including absence, myoclonic, and simple and complex partial seizures. Early myoclonic and absence seizures are associated with poor cognitive outcomes. Seizures are typically prolonged, with status epilepticus being common in DS, and pharmacological management is difficult. Seizures may lessen in severity after puberty, but rarely cease.

Initial EEG can be normal or show nonspecific changes, which makes DS difficult to diagnose. Later on, epileptiform activity appears (e.g., generalized spike and wave discharges, multiple spike and wave discharges, and multifocal spikes). Brain MRI is typically normal or may show mild generalized atrophy and/or hippocampal sclerosis.

Developmental Delay

Individuals generally have a period of normal development prior to onset of seizures. After seizure onset, children often develop delays in language and communication with severe learning difficulties. In addition, they may demonstrate motor delays, poor growth, poor balance, low muscle tone, and impaired dexterity. Older children with Dravet Syndrome will develop a “crouched gait” and may require assistance with mobility as adults.

Behavioral Disturbance

Individuals with Dravet Syndrome often have ADHD-like phenotype characterized by impulsivity, inattentiveness, hyperactivity, and distractibility. This is thought to be possibly related to the inability of the GABA system to provide negative feedback to extraneous sensory input, making them less responsive to conventional stimulant medication. Children with DS often also exhibit traits associated with autism (ASD) including stereotyped behaviors and social interaction deficits.

Other Medical Concerns

Children with DS also often experience sleep disturbances that are severe and persistent. These sleep disturbances are common among many developmental epilepsy syndromes and involve altered circadian rhythms. They can also exhibit eating, growth, and nutritional concerns often requiring a gastrostomy tube for feeding, and can also experience frequent infections. Children with DS have good life expectancy, with an 85% chance of surviving into adulthood. Some children do develop severe disabilities with associated medical problems that affect their lifespan. Additionally, children with DS are at a higher risk of Sudden Unexplained Death in Epilepsy (SUDEP) compared to children with other types of epilepsy syndromes. This may be related to subtle changes in heart regulation, as the *SCN1A* gene is also used by cells in the heart.

Diagnosis

Dravet Syndrome is a clinical diagnosis. Core features include refractory epilepsy characterized by multiple different seizure phenotypes, progressive neurodevelopmental delay and neurologic disability that begin with first seizure onset, and persistent dysfunction in cognition and motor skills that persist into adulthood. It is recommended that genetic testing is pursued to support the clinical diagnosis and offer guidance to the family.

Genetics

About 80% of Dravet Syndrome is caused by *de novo* genetic mutation in the alpha-1 subunit of voltage-gated calcium channel gene (*SCN1A*) on chromosome 2q24. There are mutations in other genes that have been associated in other developmental and epileptic encephalopathies that present similarly to Dravet Syndrome.

Molecular Etiology

SCN1A codes for an alpha subunit of a voltage-gated sodium channel (VGSC). The alpha unit is transmembrane and forms the central pore for the ion channel, responding to voltage differences allowing the flow of sodium ions in accordance with electrochemical gradients. The influx of sodium ions, and thus, the appropriate opening and closing of the channel, is essential for the generation and coordination of action potentials throughout the nervous system. Decrease in VGSC function can lead to a reduction in sodium currents, which then impairs signaling to the brain. VGSCs have been shown to play a central role in the etiology of epilepsy, and is therefore a target of many antiepileptic drugs.

Genetic Testing

The recommended molecular genetic testing is an epilepsy multigene panel, which includes *SCN1A* and other genes of interest, as is most likely to determine the genetic cause of the condition while limiting variants of uncertain significance or other pathogenic variants not related to the underlying presentation. Single-gene testing of *SCN1A* is often not useful and is not recommended. Whole exome sequencing studies could also be considered as first line testing.

Genotype-Phenotype Correlations

Mutations *SCN1A* are also responsible for other epilepsy diseases (e.g., West syndrome, Rett syndrome, Lennox-Gastaut syndrome), as well as non epilepsy diseases. There is some limited correlation between the type of mutation and the resulting phenotype. In general, variants that truncate or completely disrupt the SCN1A protein often lead to Dravet syndrome (a more severe childhood epilepsy syndrome), while missense variants lead to less severe phenotypes of childhood epilepsy. In addition, de novo mutations (not inherited from the parents) are more common in those with more severe phenotypes such as Dravet syndrome, while inherited variants are more likely in less severe phenotypes. However, *SCN1A* gene testing is not predictive, as it displays variable expressivity in which patients with the same variants can present with a broad range of phenotypes.

Genetic Counseling

SCN1A variants are inherited in an autosomal dominant pattern, where each child of a parent with a disease-causing mutation has a 50% chance of inheriting that disease-causing mutation. However, 80% of Dravet Syndrome is caused by *de novo* mutations, in children with no family history of the condition or variant. There has been some report of somatic and germline mosaicism of *SCN1A* variants, which may increase the recurrence risk for families in which the child has an apparent *de novo* mutation. Genetic counseling and potential familial testing is recommended in all instances where an SCN1A mutations is identified.

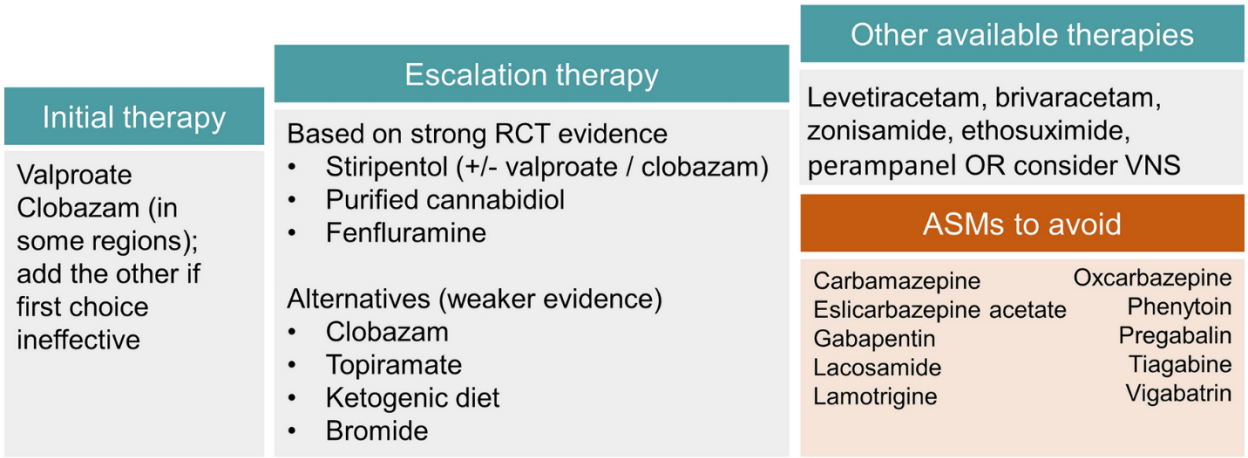
Treatment and Management

Therapy in Dravet Syndrome focuses on antiepileptic medications that bind the GABA receptors. First line pharmacotherapies are valproic acid and clobazam, however, seizures associated with DS are often refractory and lead to trials of other therapies. An overview of antiepileptic drugs therapy is outlined below.

Other forms of management include ketogenic diet therapy, surgical therapies such as vagus nerve stimulation or deep brain stimulation. There are anecdotal claims regarding medical cannabidiol/marijuana, but there has been no proven efficacy.

In addition to seizure management, it is important to address the comorbidities of DS by involving specialists in PT/OT, sleep medicine, behavior and development, gastrointestinal, cardiology, etc. as needed to support the needs of each individual child.

Figure 1. Treatment pathway in patients with Dravet syndrome.



From: A Practical Guide to the Treatment of Dravet Syndrome with Anti-Seizure Medication

Patient Support Resources

1. **Dravet Syndrome Foundation**
   Phone: 203-392-1950
   Fax: 203-907-1940
   Email: info@dravetfoundation.org
   www.dravetfoundation.org

2. **Epilepsy Foundation**
   Phone: 800-332-1000; 301-459-3700
   Email: ContactUs@efa.org
   www.epilepsy.com

3. **National Institute of Neurological Disorders and Stroke (NINDS)**
   PO Box 5801
   Bethesda MD 20824
   Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
   Febrile Seizures Fact Sheet

4. **American Epilepsy Society**
   www.aesnet.org

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About the RCPU:

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20, F.S., of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate disorders of intellectual disability through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects. Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health.

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