Developmental assessments should begin as early as possible and should be repeated regularly. Ideally, children with Dravet syndrome should be followed by a neurodevelopmental psychologist or pediatrician.

Early implementation of global therapies is essential to support optimal development. Children with Dravet syndrome should receive physical, occupational, speech, and social/play therapies and an enriched environment is encouraged.24

A number of co-morbid conditions appear to be commonly associated with Dravet syndrome and are currently under further investigation.25,26,27 Preliminary data suggests that children with Dravet syndrome may be at increased risk for:

- Orthopedic conditions, including but not limited to, pes planus/pes valgus foot deformities, neurogenic scoliosis and crouch gait25,26
- Chronic upper respiratory infections and otitis media25
- Low humor immunity
- Sensory integration disorders and other autism spectrum characteristics26
- Growth and nutrition issues
- Dysautonimia, including difficulty with temperature regulation, decreased sweating, intermittent tachycardia and slowed GI motility27

Improve the Outcome

Implement early intervention therapies, enriched environment, and developmental assessments to help ensure patient reaches optimal potential. Monitor for comorbid conditions.

References
Introduction
Dravet syndrome, also referred to as Severe Myoclonic Epilepsy of Infancy (SMEI), is a catastrophic epileptic encephalopathy that begins in the first year of life in previously healthy children. It was first described by Charlotte Dravet in 1978 and has been recognized as a syndrome by the International League Against Epilepsy since 1989. Initial symptoms typically include prolonged, febrile, clonic or unilateral convulsions, which may progress to frequent status epilepticus. Later on, seizures occur without fever. Between the ages of 12 and 48 months, other seizure types emerge, commonly myoclonic, partial and atypical absence. Progressive slowing of psychomotor development, which may include regression of acquired skills, also becomes apparent during this timeframe. Initial EEGs are usually normal, but generalized multifocal spikes and spike-wave discharges later appear. Photosensitivity is observed in about 42% of patients, though it is often transient. Other neurologic signs, such as ataxia, may also appear. The mortality rate is estimated at 16% and is usually attributed to accident, complications of a seizure, or sudden unexplained death in epilepsy (SUDEP).

Epidemiology
Dravet syndrome is a rare disorder. Initial estimates from the 1990’s place the incidence at one per 40,000° and one per 20,000 representing 3% to 5% of all severe epilepsies beginning in the first year of life. However, given improved recognition of this disorder, new epidemiologic studies are needed to confirm these numbers.

Genetics
SCN1A is currently the most clinically relevant gene known to cause epilepsy. Mutations in the α1 subunit of this neuronal voltage-gated sodium channel gene are associated with a variety of phenotypes, including SMEI, SME Borderline (SMEB), Intractable Childhood Epilepsy with Generalized Tonic Clonic Seizures (ICEGTC) and Generalized Epilepsy with Febrile Seizures Plus (GEFS+). Research continues to expand the phenotypic variability and it has been suggested that Dravet syndrome is the severe form of a broader clinical spectrum. Mutations in SCN1A contribute to up to 8% of reported cases of Dravet syndrome, which may progress to frequent status epilepticus. Later on, seizures occur without fever. Between the ages of 12 and 48 months, other seizure types emerge, commonly myoclonic, partial and atypical absence. Progressive slowing of psychomotor development, which may include regression of acquired skills, also becomes apparent during this timeframe. Initial EEGs are usually normal, but generalized multifocal spikes and spike-wave discharges later appear. Photosensitivity is observed in about 42% of patients, though it is often transient. Other neurologic signs, such as ataxia, may also appear. The mortality rate is estimated at 16% and is usually attributed to accident, complications of a seizure, or sudden unexplained death in epilepsy (SUDEP).

When an infant presents with more than one prolonged febrile seizure during the first year of life, ordering SCN1A gene testing will help confirm diagnosis of Dravet syndrome and aid in optimizing treatment. To one large study, a higher rate than any other phenotype. Of the many SCN1A mutations described in patients with Dravet syndrome, the majority arise de novo and at least 50% are of a type (frameshift, nonsense, insertion, deletion) predicted to result in protein truncation with haploinsufficiency. Related genotype to phenotype has proven challenging. While truncating mutations occur almost exclusively in SMEI, missense mutations have been detected in both mild and severe phenotypes. Microdeletions on chromosome 2q involving SCN1A are another cause of Dravet syndrome, and are easily missed by standard DNA sequencing techniques. Modifying genes and environmental factors likely play an important role in clinical outcome. Research is ongoing to identify additional factors that contribute to the severity of the Dravet syndrome phenotype.

Differential Diagnosis
As the initial seizures are often associated with fever, distinction from benign febrile convulsions is important. In Dravet syndrome: (1) the seizure type is frequently clonic or hemi-clonic rather than generalized tonic-clonic; (2) the seizures are more prolonged and frequent, even when treated; and (3) hyperthermia is a triggering factor even when temperature is moderate. The diagnosis is confirmed when other seizure types emerge, EEG, CT, MRI and metabolic studies are usually normal initially. EEG pattern, age of onset and initial seizure semiology distinguish SMEI from Lennox-Gastaut syndrome. Myoclonic-Astatic Epilepsy (MAE) may be more difficult to distinguish early in the course of the disease. The course of other sodium channelopathies such as GEFS+ and ICEGTC is similar to that of SMEI prior to the onset of multiple seizure types and developmental decline. A majority of cases of Dravet syndrome will test positive for an SCN1A gene mutation, making testing a useful diagnostic tool. However, a negative test does not preclude the diagnosis, which should be made clinically.

Treatment
Avoid medications which may aggravate seizures in Dravet syndrome. These include: lamotrigine (Lamictal®), felbamate*, fosphenytoin* (Diphenylhydantoin Phosphate), phenytoin infusion, ethosuximide, felbamate, and topiramate* (Topamax®). Carbamazepine* and valproate do not appear to affect the SMEI clinical outcome. Topiramate* decreases status epilepticus, vigabatrin, titanium, and clobazam improve seizure control.

Improve the Outcome
Employ treatment regimens that have proven efficacy. Develop and implement seizure management protocols. Instruct parents to avoid seizure triggers and to manage the syndrome acutely. Please visit the IDEA League’s online professional forum for dosing recommendations from our Professional Advisory Board as well information on importing these medications.

Consider treatments which may be helpful in Dravet syndrome, but which require further study. These include: vitamin B6 therapy, IVIG therapy, ethosuximide, zonisamide (Zonegran, Ezcar gran®) and vagus nerve stimulation (VNS).

Implement an aggressive acute seizure management protocol and encourage parents to adhere to it. The protocol should include a fast-onset benzodiazepine (diazepam, midazalam, nasal versed, buccal lorazepam) or paraldehyde for any convulsive seizure lasting longer than five minutes, and instructions for when to call for emergency dispatch, as well as when to transport to a medical facility. Written hospital seizure protocols should also be determined and are beneficial for patients to have with them all times.

Instruct parents to manage the syndrome on a day-to-day basis by avoiding seizure triggers. Common triggers in Dravet syndrome include mild to moderate hyperthermia (as from fever, exertion, environmental conditions, or warm baths), illness, stress, flickering lights, and patterns. Prevent fevers as able; treat them immediately and appropriately as they occur.

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