**Dravet Syndrome: Diagnosis and Long-Term Course**

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**ABSTRACT:** Dravet syndrome is one of the most severe epilepsy syndromes of early childhood, and it comes with very high morbidity and mortality. The typical presentation is characterized by hemiclonic or generalized clonic seizures triggered by fever during the first year of life, followed by myoclonic, absence, focal and generalized tonic-clonic seizures. Non-convulsive status epilepticus and epileptic encephalopathy are common. Development is normal in the first year of life, but most individuals eventually suffer from intellectual impairment. Dravet syndrome is associated with mutations in the sodium channel alpha1 subunit gene (SCN1A) in 70-80% of individuals. SCN1A mutation results in inhibition of the GABAergic inhibitory interneurons, leading to excessive neuronal excitation. The “interneuron hypothesis” is the current most accepted pathophysiological mechanism of Dravet syndrome. The mortality rate is increased significantly in Dravet syndrome. Ataxia, a characteristic crouched gait and Parkinson’s symptoms may develop in some individuals. It is likely that Dravet syndrome is underdiagnosed in adults with treatment-resistant epilepsy. Early diagnosis is important to avoid anti-seizure medications that exacerbate seizures.

**Keywords:** Dravet syndrome, electroclinical features, comorbidities, prognosis

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**INTRODUCTION**

Dravet syndrome (previously known as “severe myoclonic epilepsy of infancy”) was first described by Dr. Charlotte Dravet in 1978.1 It is an early-onset treatment-resistant epilepsy syndrome that typically presents during the first year of life. The incidence of Dravet syndrome is estimated at 1 per 22,000-40,000 based on studies in the United Kingdom and Denmark,2,3 and it affects males twice as often as females. It typically causes an epileptic encephalopathy. In 2001, Claes and colleagues4 discovered mutations in the sodium channel alpha1 subunit gene SCN1A in seven individuals with Dravet syndrome. SCN1A mutations, usually de novo, are found in 70 to 80% of patients with Dravet syndrome. It is now appreciated that the electroclinical features of Dravet syndrome are broader than the original description and that the myoclonic seizures or generalized spike and wave are not present in all patients. Focal seizures that may evolve to generalized convulsive seizures are the dominant seizure type in some individuals and are associated with multifocal EEG abnormalities. With the wider application of new genomic technologies in the diagnosis of epilepsy of unknown cause, it is recognized that other genetic abnormalities (PCHD19, GABRG2, SCN1B and SCN2A) may cause a similar phenotype as Dravet syndrome.

**CLINICAL PRESENTATION AND EVOLUTION OF EPILEPSY IN DRAVET SYNDROME**

Seizure onset is typically in the first year of life, with prolonged, febrile and afebrile hemiclonic or generalized clonic seizures in previously healthy children. They may be associated with vaccinations or hyperthermia, including a warm bath. Over the subsequent months, affected individuals experience recurrent febrile and afebrile seizures that often affect alternate sides of the body. Between one and four years of age, other seizure types develop, including myoclonic and atypical absences, focal seizures and generalized tonic-clonic seizures. Focal seizures, with or without impairment of awareness, may be associated with such prominent autonomic features as pallor, cyanosis and drooling, and may evolve into a focal motor or bilateral convulsive seizure. Tonic seizures are reported to be uncommon in Dravet syndrome. In some individuals, myoclonic seizures do not develop and other seizure types, particularly focal or multifocal seizures, are the predominant seizure types.

In a retrospective survey5 of 138 children with Dravet syndrome with SCN1A mutations from China, seizure onset was before the age of 7 months in 77%. 72% of the children in that study had febrile seizures with a duration longer than 15 minutes, and 67% had two or more febrile seizures within a 24-hour period. Seizures were hemiconic with fever in 80%. In a study of 96 children who had febrile seizures prior to one year of age, 46 of whom had Dravet syndrome and 50 of whom did not, the factors that correlated significantly with Dravet syndrome were onset of febrile seizures under the age of 7 months, 5 or more seizures, duration of seizures longer than 10 minutes, hemiconvulsions, focal seizures, myoclonic seizures and hot-water-induced seizures.6 Reflex seizures are frequent, and the most common trigger is hyperthermia...
Status epilepticus occurs commonly in Dravet syndrome, both
the convulsive and non-convulsive types. Non-convulsive status
epilepticus is also described in the literature as “obtundation
status epilepticus.” Obtundation status epilepticus is characterized
by altered awareness, autonomic symptoms and subtle myoclonus
that commonly involves the fingers and orobuccal muscles, and it
may last for many hours or days. Status epilepticus may be life
threatening, and the symptoms and signs of non-convulsive status
epilepticus may be subtle and difficult to appreciate. Thus, it is of
utmost importance to educate parents and caregivers about the
early symptoms and signs of non-convulsive status epilepticus. It
is also very important to put an individualized emergency (rescue)
management plan in place for each individual so as to facilitate
early intervention to prevent prolonged status epilepticus and its
associated complications.

With respect to the evolution of epilepsy over time, seizures
tend to become less frequent and severe in adolescence and
adulthood. Fever sensitivity persists but has less impact. Myoclonic,
atypical absence and focal seizures with altered awareness are
less common in adulthood. The most common seizure type in
adulthood is generalized tonic-clonic, which may be focal in onset
and occurs mainly during sleep. Patients may also experience
bilateral or asymmetrical posturing, which may be followed by
tonic vibratory or clonic movements. However, there are few
studies that describe in detail the electroclinical features of the
seizure types in Dravet syndrome during adolescence or adult-
hood. Ictal recordings of five adults revealed subclinical focal
seizures in three, focal seizures that evolved into bilateral con-
voluntary clonic seizures in three, obtundation status in one and
tonic events in another patient. In a long-term study of 53 children aged 4 to 14 years
who were followed for from 3 to 14 years, seizure frequency was
weekly in 74%, monthly in 13% and daily in 13%. The most
common treatments employed in this study were valproic acid,
clobazam and a ketogenic diet.

Takayama and colleagues described 64 patients followed at
one epilepsy center in Japan. The median age at last follow-up was
30 years (range = 19-45), and only 1 of 44 individuals with typical
Dravet syndrome was in remission, in contrast with 4 of 20 indi-
viduals with atypical Dravet syndrome. In this study, atypical
Dravet syndrome was characterized by absence of myoclonic and
atypical absence seizures.

EEG Evolution in Dravet Syndrome

The EEG is typically normal during the first year of life. Subsequently, the EEG background may be normal or slow. Sleep
architecture is typically preserved. Generalized spike and wave,
polyspike wave and multifocal spikes are common.

Few studies have carefully documented the evolution of EEG
findings over time in Dravet syndrome. Specchio and colleagues described EEG findings in 22 children with Dravet syndrome over
the first five years following diagnosis. In all these children, the
EEG background was normal, but background slowing was seen in
27% after six months. Epileptiform discharges were present in
27% at seizure onset and in 64% by 5 years follow-up. Multifocal
epileptiform discharges were observed in 57%, focal epileptiform
discharges in 29%, and 14% had generalized epileptiform
discharges. A photoparoxysmal response was seen in 9% at
seizure onset and in 41% by the end of the study. In a study of
16 children, Korff et al. reported that the EEG was abnormal in
81%. However, at the time of seizure onset, the EEG was abnor-
mal in only 25% of the children. The most common epileptiform
pattern consisted of generalized spike wave discharges.

In a study of 23 patients in whom seizures were recorded during video-EEG monitoring, Kim and colleagues divided patients into three groups: 0-5 years (n = 7), 6-10 years (n = 11) and 11 years and older (n = 5). Slowing of the EEG background was more common in older patients and a photoparoxysmal response in younger children. Epileptiform discharges were found in most patients, and the most common pattern was multifocal
epileptiform discharges.

Nabbout et al. also described five adolescents with Dravet
syndrome who had bifrontal spike and slow wave and generalized
fast polyspikes in sleep, features similar to Lennox–Gastaut
syndrome. In another study of EEG evolution in 24 patients with
Dravet syndrome, Genton et al. described normal EEG background in 8 and slow and disorganized background in 11. Epileptiform activity was multifocal in 11, focal in 7 and
generalized in 6. Photosensitivity and pattern sensitivity tended to
appear by 20 years of age.

There is still an opportunity to add to the literature on the
evolution of the electroclinical features of Dravet syndrome with SCN1A mutations over time, and additional ictal EEG data would
be very informative.

Family History of Epilepsy/Febreile Seizures

The first report of SCN1A mutations in epilepsy was in the
syndrome of genetic epilepsy with febrile seizures plus. A
family history of epilepsy or febrile seizures has been observed in
15-35% of individuals with Dravet syndrome, and the most
common phenotype seen in affected relatives is genetic epilepsy
with febrile seizures plus. Dravet syndrome has been reported in
monozygotic twins and rarely in zygotic twins. There are also rare
reports of two or more affected children in the same family.
Somatic or germline mosaic mutations may explain an unaffected
or mildly affected parent, and in one study mosaicism was found in
7% of families with Dravet syndrome. The observation of a
positive family history of febrile seizures and epilepsy in indivi-
duals with Dravet syndrome and de novo mutations in SCN1A
suggest that the mode of inheritance is polygenic and that other
modifier genes such as SCN9A contribute to the phenotype.

Genetic Testing in Dravet Syndrome

The first mutations in the SCN1A gene in seven individuals
with Dravet syndrome were discovered by Claes and colleagues
in 2001. It is now recognized that SCN1A mutations are seen in
75-80% of individuals with Dravet syndrome. More than 500
mutations have been reported in individuals with Dravet syn-
drome. Mutations are truncating in 40-50%, missense in 40% and
splice site in the remainder. Whole-gene deletions are observed in
2-3%, and gene duplications are rare. Most gene mutations are de
novo, but familial mutations occur in 5-10% and are usually
missense.

Truncating, nonsense and frameshift mutations and gene
deletions correlate with the classical Dravet syndrome phenotype
with an earlier age at onset. Missense mutations that affect
The phenotype of SCN1A mutations may be heterogeneous even within the same family, and it is likely that modifying genes are important in determining the severity of epilepsy and possibly comorbidities. In animal models, SCN8A may restore a normal seizure threshold in the presence of SCN1A mutations. The compensatory up-regulation of SCN3A may mitigate the effects of Nav1.1 deficiency. Variants in CACNA1A genes may also modify the phenotype in Dravet syndrome. In a study of 48 patients with Dravet syndrome and SCN1A mutations, CACNA1A variants were observed in 20 subjects. In individuals with CACNA1A variants, absence seizures, earlier age at seizure onset and more frequent prolonged seizures before the age of one year were more common than in individuals without CACNA1A variants. SCN9A mutations have also been observed in some individuals with SCN1A mutations and may be associated with a more severe clinical phenotype.

In children where SCN1A mutations are not found, several other genes have been reported, including CHD2, GABRA1, GABARG2, STXBP1, SCN1B, SCN2A and PCDH19. However, the electroclinical phenotypes associated with these other gene abnormalities are often somewhat atypical for Dravet syndrome. With the wider application of next-generation sequencing in the evaluation of epilepsy of unknown cause, it is likely that the electroclinical features associated with gene mutations other than SCN1A will be better described.

### Pathophysiology of Dravet Syndrome

Several pathophysiological mechanisms have been reported in Dravet syndrome, and the most accepted is the “interneuron hypothesis,” where SCN1A mutations result in inhibition of the GABAergic inhibitory interneurons, resulting in excessive excitation. This mechanism is supported by a mouse model. Nav1.1 was preferentially expressed in the axon initial segments of the parvalbumin-positive interneurons, the main type affected in Dravet syndrome. Studies using models involving human-derived induced pluripotent stem cell neurons suggest that both GABAergic inhibitory neurons and glutamatergic excitatory neurons in the forebrain of patients with Dravet syndrome are hyperexcitable with increased sodium current density, overall resulting in network hyperexcitability. SCN1A haploinsufficiency may result in a compensatory increase in the sodium current via expression of other sodium channels.

### Neuroimaging in Dravet Syndrome

Structural brain imaging using MRI is usually normal in Dravet syndrome, but imaging abnormalities are described in some patients. In a review of 120 patients in Italy with Dravet syndrome, malformations of cortical development were detected in 4. In another study, 18 children with Dravet syndrome who had MR imaging after 3 years of age, 7 had hippocampal sclerosis or loss of grey–white definition in the temporal lobe. In a study comparing nine patients with Dravet syndrome and SCN1A mutations and nine controls without seizures, globally reduced grey and white matter volumes were seen in individuals with Dravet syndrome.

### Neurodevelopment in Dravet Syndrome

Neurodevelopment and formal neurological examination are typically normal at the time of seizure onset. However, there is slowing of the rate of the developmental progress along with variable decline in the developmental quotient over time. Ataxia and pyramidal signs were present in 59 and 22% of subjects, respectively. Attention, visual/motor integration, visual perception and executive function are impaired, whereas language may be less involved in some patients.

In a study of 21 children aged 6 to 10 years with Dravet syndrome, seen at a single institution and assessed using the WISC and Vineland Adaptive Behaviour scales, no child had a normal IQ after the age of 6 years. Only 5 of the 21 children had a verbal or non-verbal IQ score greater than 60. The children had attention problems, impulsivity, perseverative responses and deficits in planning. Socialization skills assessed using the Vineland scale were significantly better than communication skills. No correlation was observed between age at seizure onset, status epilepticus, number of seizures, myoclonic or absence seizures with IQ. Nabbout and colleagues reported cognitive findings in 67 children with Dravet syndrome, 52 of whom were tested only once and 15 underwent repeat testing. IQ was typically normal before the age of 2 years (mean = 80) but low after age 3 years (mean = 48, range = 30-69). However, there was no evidence of regression. Attention and hyperactivity were common. No significant correlation was seen between IQ and age at first seizure, number of episodes of status epilepticus, or myoclonic and focal seizures. However, IQ was lower in those with SCN1A mutations. Thus, it was the conclusion of the authors that the encephalopathy was not a pure consequence of epilepsy but that the SCN1A mutation played an additional direct role.

Genton and colleagues reported 24 patients with Dravet syndrome followed to 20-50 years of age. Only three individuals lived independently, and the remainder had moderate to severe delay. Ataxia was seen in nine, dystarthis in eight and tremor in seven. In another report of 31 patients, only 1 lived independently, 7 had no language and 9 spoke only a few words. Catarino et al. described the long-term follow-up in 22 adults followed to...
COMORBIDITIES IN DRAVET SYNDROME

A crouched gait has been described in many reports on Dravet syndrome. In one study, utilizing formal gait analysis in patients with Dravet syndrome who ranged in age from 2 to 3 years, a crouched gait was seen in 8 out of 9 children aged 13 years and older, in 50% of children aged 6-12 years and in no child younger than 6 years. Fasano and colleagues, in a study of 12 adults with Dravet syndrome, described features of Parkinsonism with bradykinesia, asymmetric rigidity and cogwheeling in 11 (91%). Two patients were treated successfully with levodopa, resulting in significant improvement in their Parkinsonian symptoms. Osteopenia and increased risk of fractures are common in individuals with treatment-resistant epilepsy, particularly when enzyme-inducing drugs are used or there is reduced mobility, but this has not been studied in Dravet syndrome.

Despite sleep concerns being a common complaint in individuals with Dravet syndrome, the literature on this topic is limited. A small, retrospective study of polysomnogram findings in six children with Dravet syndrome referred for sleep assessment found no abnormalities in sleep macroarchitecture despite parental concerns.

SUDEP and Mortality

Mortality is increased significantly in Dravet syndrome, and death may occur at any age but is more frequent during childhood. Death may be due to status epilepticus, SUDEP or accidental death, and it may also be related to seizures associated with drowning or injury. Mortality rates have varied in reported studies from 3 to 20.8%, with deaths due to sudden, unexpected death of someone with epilepsy (SUDEP), status epilepticus and accidents (especially drowning) being the most common. In a report based on data from a patient support group, it was estimated that individuals with Dravet syndrome have a risk of SUDEP approximately 15-fold higher than those with other childhood epilepsies.

Studies in Dravet mice models suggest that SUDEP is due to increased parasymptomatic activity after a generalized tonic-clonic seizure, resulting in lethal bradycardia and electrical ventricular dysfunction. As this finding was seen in mice with the SCN1A mutations selectively targeted to affect the brain, but not if the SCN1A mutations were selectively targeted to affect the heart only, it was proposed that SUDEP is due to a brain effect on the heart after a seizure. Cheah and colleagues proposed that the natural decline in Nav1.3 channel expression with the failure of increase in Nav1.1 channel expression leads to a disinhibition of neuronal circuits, treatment-resistant epilepsy and premature death. In a study of mice with an SCN1A mutation, Auerbach observed a twofold increase in sodium current density in ventricular myocytes, resulting in increased excitability, prolongation of action potential duration, which results in QT prolongation, abnormal rhythms and spontaneous deaths in some mice. Thus, it is possible that altered electrical cardiac function may increase the risk of SUDEP, but these animal data have not been confirmed in humans.

CONCLUSION

Dravet syndrome remains one of the most severe epilepsy syndromes of early childhood and is characterized by very high morbidity and mortality. It impacts physical and cognitive function, mental health, bone health and sleep. Anxiety about the risk of death and SUDEP is very high in parents and caregivers. Early diagnosis of Dravet syndrome is important to avoid anti-seizure medications that exacerbate seizures, but there is a major need for new therapies to improve seizure control and long-term outcomes.

Transition from paediatric to adult services is very challenging, and there is a great need to improve this process. It is also likely that Dravet syndrome is underdiagnosed in adults with treatment-resistant epilepsy. It is therefore important to educate colleagues who are caring for adults about this epilepsy syndrome.

DISCLOSURES

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