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Dravet Syndrome: Inroads into Understanding Epileptic Encephalopathies

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Dravet syndrome is a severe childhood epilepsy characterized by intractable seizures and neurodevelopmental delay. First described in 1978 by Dravet as severe myoclonic epilepsy of infancy (SMEI), the syndrome was renamed in light of the widening spectrum of clinical phenotypes associated with the more-recently discovered underlying genetic basis. Based on clinical diagnostic criteria, Dravet syndrome has been estimated to affect 1 in 40 000 children, accounting for about 7% of severe epilepsy occurring in children under age 3 years.[1] These numbers likely underestimate the actual incidence, given that genetic testing has dramatically increased diagnosis of this disorder.

Dravet syndrome has been mainly associated with mutations in a neuronal voltage-gated sodium channel gene, *SCN1A* (*sodium channel subunit 1A*).[2-5] *SCN1A* mutations also have been associated with febrile seizures (FS) and milder forms of epilepsy, and more recently, *SCN1A* polymorphisms have been implicated in susceptibility to FS.[6] Unravelling the mechanisms of epileptic seizures in Dravet syndrome is of great importance, because *SCN1A* mutations confer varying degrees of seizure susceptibility, in part determining the seizure threshold. The recent association of this childhood epilepsy with the occurrence of vaccine-related seizures and encephalopathy has led to a reexamination of this historically charged medicolegal controversy.[7]

An animal model for Dravet syndrome has reproduced many of the clinical features and has expanded our understanding of how seizures occur in this syndrome.[8] The most greatly affected neurons appear to be interneurons, which serve as part of the inhibitory circuitry in the brain. The emerging concept of epilepsy resulting from interneuron dysfunction, or "interneuronopathy," has been useful in understanding the mechanisms of seizures in Dravet syndrome.[8]

Dravet syndrome is recognized as an epileptic encephalopathy because of the association between frequent seizures and cognitive impairment and poor developmental outcome. The effect of seizures on the developing brain is of great interest and critical importance in the field of pediatric epilepsy.

EEG	Electroencephalography
FS	Febrile seizure
GABA	Gamma aminobutyric acid
GEFS+	Generalized epilepsy with febrile seizures plus
SCN1A	*Sodium channel subunit 1A*
SMEB	Severe myoclonic epilepsy borderline
SMEI	Severe myoclonic epilepsy of infancy
SUDEP	Sudden unexplained death in epilepsy

History

Dravet syndrome was first described by French pediatric neurologist Charlotte Dravet in 1978.[9] She named the syndrome "severe myoclonic epilepsy of infancy" and delineated the main clinical features. Dravet followed a large cohort of children with SMEI and described its natural history in subsequent publications. Others later added to the description of clinical features. A "borderline" phenotype, designated severe myoclonic epilepsy borderline (SMEB), describes children who lack one or another of the classic features of Dravet syndrome but who fall into the more severe end of the clinical spectrum.[9-14]

In 1997, the genetic pedigree for a familial epileptic syndrome known as generalized epilepsy with febrile seizures plus (GEFS+) was described.[15] A mutation in *SCN1B* was identified.[16] Additional mutations were subsequently described in the *SCN1A* gene (and, rarely, in *SCN1B* and gamma aminobutyric acid [GABA] receptor genes), establishing a polygenic basis for GEFS+.[17,18] The GEFS+ phenotype involves a susceptibility to FS extending beyond the usual 5- to 6-year age limit, and, in some individuals, afebrile seizures. GEFS+ is generally associated with an excellent neurologic outcome and does not carry a lifelong risk of seizures for most affected individuals. It was observed, however, that relatives of GEFS+ individuals occasionally had severe epilepsy syndromes, including Dravet syndrome. Subsequently, Dravet syndrome was discovered to have a molecular basis in common with GEFS+, involving sodium channel subunit 1A mutations.[19] Based on this finding, the spectrum of epilepsies associated with neuronal sodium channel mutations expanded rapidly, with Dravet syndrome representing the severe end of the spectrum as well as the most common epilepsy associated with mutations in the *SCN1A* gene.[20-28]

The spectrum of epilepsies associated with *SCN1A* mutations is as follows:

FS———GEFS+———SMEB—Dravet syndrome (SMEI)
(mild)————————————————————(severe)

Clinical Features

The clinical features of Dravet syndrome include onset of prolonged FS in the first year of life, with normal development and electroencephalography (EEG) results, and emergence

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in the second year of life of afebrile seizures, abnormal EEG findings, and developmental stagnation or regression. Affected children have a variety of seizure types, including myoclonic, atonic, generalized tonic-clonic, absence, complex partial, and, less often, tonic. Frequent episodes of status epilepticus, ongoing susceptibility to hyperthermia-induced seizures, and pharmacoresistance are other key clinical features. Stimulus-provoked seizures occur frequently, most often manifesting as light (photic) sensitivity but also including stress (eg, when a toddler is chastised).[1,10] There is considerable variety in the phenotype, with up to one-third of children having an initial afebrile seizure or generalized tonic-clonic status epilepticus instead of the more common hemiclonic febrile status epilepticus, some children demonstrating little to no cognitive decline, and other having more delayed onset of afebrile seizures and EEG deterioration.[1]

Over a lifetime, seizures tend to evolve between age 1 and 4 years, various seizure types occur (as described earlier), and episodes of status epilepticus with fever as well as episodes of nonconvulsive status epilepticus are not infrequent. After age 5 years, convulsive status epilepticus tends to be less frequent, and nocturnal generalized tonic-clonic seizures predominate. Adults show persistence of seizures and fever susceptibility; nocturnal generalized tonic-clonic is the predominant seizure type, and typically far fewer absence and myoclonic seizures are seen.[1,13]

Mortality is estimated at 15% by age 20 years, as a complication of status epilepticus, accidents, and sudden unexpected death in epilepsy (SUDEP). A surprising number of pediatric SUDEP cases have been reported in children with Dravet syndrome, possibly related to a function of *SCN1A* in the heart.[1,29] Defects in the neuronal sodium channel expressed in the heart may predispose to epilepsy-related arrhythmias and conduction disturbances. There is also a connection between prolonged QT interval and SUDEP; a QT dispersion has been described in children with epilepsy, along with an ictal A-V nodal block or bradycardia possibly linked to increased risk of SUDEP.[29]

Development is typically normal until the second year of life, but late walking and delayed acquisition or even regression of language (especially after status epilepticus) are frequently seen.[1,10,14] Seizure severity at an early age has been associated with more severe developmental delay.[10] Children with Dravet syndrome are often hyperkinetic, and attentional disorders are common. Oppositional behaviors are common between 7 and 20 years of age.[28] Long-term cognitive outcome is poor, with most children's IQ in the mental retardation range. Better cognitive outcome has been associated with fewer seizures (<5/month) and fewer episodes of status epilepticus.[10,14] The developmental quotient decreases over a period of several years and then tends to stabilize at around a value of 40 in most children.

In the motor domain, a peculiar gait abnormality, termed "crouched gait," may develop and worsen in adolescence; this gait appears to involve mild ataxia along with increasing spasticity in the lower extremities.[30] Ataxia has been reported in 59% of children with Dravet syndrome.[28]

Molecular Genetics

Dravet syndrome is associated mainly with mutations in the *SCN1A* gene, which codes for a pore-forming subunit of a neuronal voltage-gated sodium channel.[2,3,31] Situated on chromosome 2 at position 2q24.3, *SCN1A* is part of a cluster of voltage-gated sodium channel genes that includes *SCN2A*, *SCN3A*, *SCN7A*, and *SCN9A*, which encode different sodium channel subunits.[4,32-34] Collectively, mutations in these sodium channel subunits have been associated with paroxysmal disorders, including epilepsy.[4] Mutations in *SCN1A* are associated with a spectrum of epileptic syndromes ranging from GEFS+, generally resulting from missense mutations,[17] to Dravet syndrome, where the mutation tends to be more deleterious (nonsense, truncating, or frameshift mutation), resulting in a loss or gain of function.[3,20,23,25-27] Haploinsufficiency of the *SCN1A* gene is the main genetic mechanism resulting in the Dravet syndrome phenotype, accounting for the majority of affected children.[11,23,25-28,41] Other abnormalities, including *SCN1A* deletions, amplifications, and duplications, occur in a minority of patients.[22,28]

More than 700 mutations in the *SCN1A* gene have been described to date.[2,3] The first identified mutations were point mutations, accounting for about 80% of affected children. Subsequently, additional mechanisms, including copy number variation (5%-10%), exon deletions/duplications (5%-10%), and microchromosomal deletions, were identified, accounting for an additional 10%-20% of cases.[2,3,35,36] Up to 95% of mutations are thought to occur de novo, and 5% are considered familial (including GEFS+ families). Parental mosaicism also has been reported in some patients.[37] Approximately 70% of children with SMEB have an *SCN1A* mutation as well. Only a few other gene mutations have been identified in patients with Dravet syndrome, with one case involving a GABA receptor mutation (*GABRG2*)[18] and some children with clinical Dravet syndrome who do not test positive for any mutation in the *SCN1A* or *GABRG2* gene.[38] A recent study demonstrated the involvement of a related sodium channel subunit 9A mutation in a number of children with clinical Dravet syndrome, some of whom had no mutation in the *SCN1A* gene.[38] Other sodium channel subunit mutations, *SCN1B* and *SCN2A*, have been described in association with Dravet syndrome.[39,40] Another study analyzed DNA from 333 patients with Dravet syndrome and found that 20% had no mutation in the *SCN1A* gene, even after examination for microdeletions.[41] The lack of a demonstrated *SCN1A* gene mutation in some children with Dravet syndrome has been explained by assuming a polygenic basis for the disorder,[2] or has been attributed to a methodological limitation of the assay used to search for mutations.[42]

Identifying genotype–phenotype correlations of *SCN1A* mutations has proven difficult. Dravet syndrome is the most common phenotype associated with mutations in the *SCN1A* gene (>75%), and if variants are included (SMEB and other severe epilepsies of childhood), *SCN1A* mutations are associated with severe epilepsy syndromes in >85% of