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Review article

Diagnosis and long-term course of Dravet syndrome

*Ingrid E. Scheffer**

Florey Neuroscience Institutes, Department of Medicine and Paediatrics, University of Melbourne, Austin Health and Royal Children's Hospital, Melbourne, Australia

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ABSTRACT

Dravet syndrome is a severe infantile-onset epilepsy syndrome with a distinctive but complex electroclinical presentation. A healthy, developmentally normal infant presents at around 6 months of age with convulsive status epilepticus, which may be hemiclonic or generalized; seizures may be triggered by fever, illness or vaccination. The infant typically has further episodes of status epilepticus every month or two, often triggered by fever. Other seizure types including focal dyscognitive seizures, absence and myoclonic seizures develop between 1 and 4 years. Atonic drop attacks and episodes of non-convulsive status may occur. Early development is normal but slows in the second year. Developmental regression may occur, particularly with status epilepticus. EEG studies are initially normal, but after 2 years they show generalized spike-wave and polyspike-wave activity with multifocal discharges. Photosensitivity may be seen. Imaging is normal or shows non-specific findings such as atrophy.

Dravet syndrome is associated with mutations of the gene encoding the alpha-1 subunit of the sodium channel, *SCN1A*, in >70% of patients. These include sequencing mutations and copy number variant anomalies; 90% of mutations arise *de novo*. *PCDH19* mutational analysis is a second-tier test for girls with a Dravet-like picture who do not have *SCN1A* mutations.

Outcome is poor, with intellectual disability in most patients and ongoing seizures. Intellectual impairment varies from severe in 50% patients, to moderate and mild intellectual disability each accounting for 25% cases. Rare patients have normal intellect. The long-term course involves ongoing, brief nocturnal convulsions and a characteristic deterioration in gait.

1. Introduction

Dravet syndrome, previously known as Severe Myoclonic Epilepsy of Infancy, is a distinctive epileptic encephalopathy beginning in infancy, which was first recognized by Charlotte Dravet in 1978.[1] It has a characteristic electroclinical picture with a specific age of onset, evolution of seizure types, EEG features and developmental course. Following the discovery in 2001 of the gene responsible for Dravet syndrome, more than 75% of patients have had their genetic basis identified through molecular testing. This enables the clinician to make a complete clinical and molecular diagnosis of Dravet

* Florey Neuroscience Institutes, Department of Medicine and Paediatrics, University of Melbourne, Austin Health and Royal Children's Hospital, Level 2, 245 Burgundy Street, Heidelberg, Melbourne, VIC 3084, Australia. Tel.: +61 3 9035 7112; fax: +61 3 9496 2291.
E-mail address: scheffer@unimelb.edu.au (I.E. Scheffer).

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syndrome, providing information to guide the choice of anti-epileptic therapy, prognostic and genetic counselling. It is likely that optimization of therapeutic modalities maximizes cognitive outcome.

2. Clinical presentation

Dravet syndrome begins in a previously healthy and developmentally normal infant, typically around 6 months of age, with the oldest cases beginning by 15 months. The infant usually presents with febrile status epilepticus, which is often hemiclonic in nature but may be generalized. Over the next six months, the baby presents repeatedly with episodes of febrile status epilepticus, and when hemiclonic attacks occur, the lateralization may alternate in different presentations.

From one to four years of age, other seizure types usually develop. These include staring episodes of two different types, which can be distinguished with careful questioning about the attacks. The most frequent are focal dyscognitive seizures (previously called complex partial seizures), in which the infant or toddler will stare for several minutes, often with pallor, oral automatisms and head and eye deviation. They are likely to cluster and may be induced by fever. The toddler may also have brief absence seizures lasting less than 10 seconds, during which time they lose awareness. Absence seizures may occur many times per day and may not be recognized. Myoclonic seizures occur in many but not all patients with Dravet syndrome; their frequency has decreased since carbamazepine has been used less frequently as treatment in children presenting with non-lesional hemiclonic seizures. Occasional patients have atonic seizures. Many children with Dravet syndrome experience episodes of non-convulsive status epilepticus, also known as "obtundation status", in which they may be less aware, drooling and unsteady for hours or days. Seizures are triggered by fever, fatigue, photic stimulation in photosensitive patients, excitement in some and occasionally even the thought of exciting activities. Photosensitivity varies with age and occurs in up to 42% of patients.[2]

Dravet syndrome has a characteristic developmental trajectory. Infants with Dravet syndrome develop normally in the first year of life. Between the first and second year their development slows and walking is often slightly delayed, at a mean age of 17 months.[3] Their physiological ataxia may take longer to resolve than in normal toddlers. Language acquisition of single words at one year is often developmentally appropriate, however after this age language development also slows. Developmental plateauing typically occurs and sometimes regression, particularly with episodes of status epilepticus.

Classical Dravet syndrome was originally differentiated from "borderline" Dravet syndrome, in which a child presented with some, but not all, of the features of Dravet syndrome. For example, the child may not have had generalized spike-wave activity on EEG, or myoclonic seizures may have been absent. Within this borderline group, there was a subgroup in which the infant presented only with convulsive or hemi-convulsive attacks; this was coined "intractable childhood epilepsy with generalized tonic-clonic seizures" by Japanese authors and "severe idiopathic generalized epilepsy of infancy" by German authors.[4,5] Formal studies of the differences between classical Dravet syndrome and the borderline type have shown that this differentiation is not clinically useful; they suggest that all forms should be encompassed under the term *Dravet syndrome*, as similar mutational rates are observed.[6,7]

3. Investigations

EEG studies are surprisingly normal in the first 1–2 years of life despite prolonged and frequent episodes of status epilepticus. From about the age of two years, the EEG starts to show generalized and multifocal epileptiform activity.

Imaging studies are often normal or may show non-specific abnormalities such as cerebral atrophy. Hippocampal sclerosis has been observed to a varying degree in different series ranging from 2% to 70% of cases; it probably occurs in about 30% of patients overall.[8,9] Given the well-known association of hippocampal sclerosis with prolonged febrile status epilepticus, it is perhaps surprising that not all patients with Dravet syndrome have this acquired lesion.

4. *SCN1A* mutations – the predominant molecular cause of Dravet syndrome

Approximately 75% of patients with Dravet syndrome have mutations of the gene encoding the alpha-1 subunit of the sodium channel, *SCN1A*.[6,10] At least 70% have sequencing abnormalities of *SCN1A*, and the remaining 3–5% have copy number variants involving *SCN1A*.[6,10–12] Copy number variants frequently involve deletions, but duplications have also been described.[13] Most patients have novel sequencing mutations with relatively few recurrent mutations. Zuberi and colleagues performed an elegant analysis of more than 800 reported *SCN1A* mutations and showed that 50% were missense mutations and had a predilection for the voltage sensor and ion pore regions of the gene.[4] Fifty percent of mutations were truncation, and when compared with missense mutations in Dravet syndrome, they were not associated with an earlier age of onset but did confer a slightly earlier mean onset of myoclonic (15 versus 18 months) and absence seizures (17 versus 27 months).[4]

Ninety percent of mutations arise *de novo* in patients, with 10% of mutations being inherited.[10] Inherited mutations are usually missense in nature and occur in a parent with a family history of mild epilepsy phenotypes consistent with Genetic Epilepsy with Febrile Seizures Plus (GEFS+).[5,14,15] The parent may be mildly affected with febrile seizures or may not be affected at all.

The observation of sibling pairs with Dravet syndrome whose unaffected parents did not share their children's *SCN1A* mutation on routine testing led several groups to discover *SCN1A* mosaicism. The parent may have germline or somatic mosaicism, leading to an increased risk of affected children in an unaffected parent.[16–19]

A recent carefully executed examination for the presence of *SCN1A* mosaicism showed that it is more frequent than

previously appreciated.[15] Depienne and co-authors found that 19 out of 177 *SCN1A* mutations were inherited in their cohort of patients with Dravet syndrome. Mosaicism was confirmed in 12 of 19 cases and ranged from 0.04% to 85% in blood cells. Low-level mosaicism was not detectable with standard techniques and required allele specific assays; the percentage of mosaicism also varied in different tissues such as sperm and blood. There was an interesting correlation between the percentage of mosaicism and how severely affected the parent was. In their cohort, parents with 18% mosaicism or less were unaffected, while those with 43% or more were increasingly more severely affected the higher the percentage of mosaicism detected.[15] These observations are critical for genetic counselling, particularly as truncation mutations were observed in mosaic parents, and could predict a more severe phenotype such as Dravet syndrome in their offspring than may be the case for missense mutations.

In 2009, 11 girls with "Dravet syndrome" were found to have a mutation of the protocadherin-19 gene, *PCDH19*.[19] A comparison of these patients with those that had classical Dravet syndrome due to *SCN1A* mutations showed significant differences (see below).

5. Other genes implicated in Dravet syndrome

5.1. *PCDH19*

A second-tier test for Dravet syndrome involves testing for mutations involving the gene protocadherin-19, *PCDH19*. Whilst this gene has been found to have mutations in girls with "Dravet syndrome", close scrutiny suggests that there are significant but subtle phenotypic differences. However, when *SCN1A* sequencing and copy number variant studies are negative, it is certainly worth performing *PCDH19* sequencing and copy number analysis.

The discovery that girls with a syndrome resembling Dravet syndrome could have *PCDH19* mutations was reported by Depienne et al. in 2009.[20] They studied a boy who was mosaic for a hemizygous 1 Mb deletion of chromosome Xq221.[20] The only gene deleted in the region was *PCDH19*. The authors then studied 73 patients with Dravet syndrome and found 11 girls with *PCDH19* mutations. A detailed phenotypic comparison of these patients with Dravet syndrome showed that the patients had a later mean onset at nine months, compared with six months in Dravet syndrome, fewer absence and myoclonic seizures and a considerably better outcome than children with Dravet syndrome. Thus these data could be reinterpreted as girls with *PCDH19* mutations actually having the disorder Epilepsy Limited to Females with Mental Retardation (EFMR), which is part of the *PCDH19* Female-limited epilepsy spectrum. EFMR is a striking disorder, which was initially observed in a large North American family and then in two Australian and two Israeli families.[21,22] EFMR is distinctive because only girls are affected and males are normal transmitting carriers. Phenotypically, girls with EFMR usually present with seizures under three years of age, although they have been reported beginning as late as five years. They present with febrile seizures in clusters of ten or more brief focal or convulsive seizures per day over several days rather than the typical hemiclonic febrile status epilepticus characteristic of Dravet syndrome. There is no doubt that there are some patients that are difficult to distinguish, but these are less common than the usual EFMR picture, which is quite distinctive. EFMR is also characterized by marked variability in cognitive outcome, with up to one-third of girls having normal intellect; the remainder is more likely to be mild to moderately impaired rather than severely disabled, which is common in Dravet syndrome, although severe cases occur in both disorders. Autistic features are more prominent in EFMR.

5.2. *GABRG2*

There is only a single report to date of a *GABRG2* mutation associated with Dravet syndrome. *GABRG2* encodes the gamma-2 subunit of the $GABA_A$ receptor. This report concerns a patient from a GEFS+ family, in which the whole family has the *GABRG2* mutation and the majority of family members are mildly affected. Therefore the mutation is likely to be only one of the genes contributing to the more severe phenotype in the individual with Dravet syndrome.[23]

5.3. *SCN1B*

A single case with a Dravet-like syndrome was associated with a homozygous *SCN1B* mutation. *SCN1B* encodes the beta-1 subunit of the neuronal sodium channel and plays a critical role in gating channel kinetics and localization of the channel to the cell membrane. The finding of a homozygous *SCN1B* mutation in a patient with Dravet syndrome has not yet been confirmed in a second patient. A review of the history of this patient showed that he did not have the typical course of a patient with Dravet syndrome, as there had been earlier deterioration in development followed by tetra-pyramidal features with pronounced global hypotonia by 13 months; the patient died three weeks later. Thus the picture was not typical of Dravet syndrome.[24]

From a molecular point of view, *SCN1A* molecular analysis should be performed first in patients who present with the characteristic electroclinical picture of Dravet syndrome. If this is negative, *PCDH19* testing is indicated in girls.

6. Long-term course

Seizures usually continue into adult life in Dravet syndrome.[25] In a study of 14 patients, all had ongoing seizures into adulthood, which typically comprised brief afebrile tonic-clonic seizures in sleep. They occurred weekly to monthly in most individuals. Seven of the 14 patients had ongoing seizures including focal dyscognitive seizures, and a few had myoclonic, absence and atonic seizures.[26] Better seizure outcome was observed for individuals who had fewer than three episodes of status epilepticus and resolution of epileptiform activity on follow-up EEG studies.[25] All but one of the 14 patients was intellectually disabled. This ranged from severe in half of them to moderate and mild in about 25%. Many had developed a deterioration in gait with age.[26]

Gait studies have shown that many patients with Dravet syndrome develop difficulty walking as they grow older. The deterioration in gait occurs at a much later age than when seizures are at their most active from six months to five years of age, and is also later than when the child's development begins to slow from 18 months of age. Gait tends to deteriorate from about nine years, when patients gradually develop a crouch pattern.[3] From a functional point of view, patients with Dravet syndrome have difficulty walking long distances, although they maintain the ability to walk around the house and short distances. They do have pyramidal signs but true ataxia is not seen; in some ways the gait appears more Parkinsonian in character.

In terms of mortality, several studies have shown that there is approximately 15% mortality by adulthood.[2] The causes of death include sudden unexpected death in epilepsy, episodes of status epilepticus followed by multi-organ failure and accidental causes.

Dravet syndrome is the prototype of a genetic epileptic encephalopathy, for which *SCN1A* molecular analysis is a diagnostic test when performed in the correct electroclinical setting. It is essential to remember that *SCN1A* mutations are also found in milder epilepsy syndromes, such as GEFS+, and may cause simple febrile seizures in a person of normal intellect. Thus the test can only be interpreted with an understanding of the clinical molecular "puzzle" of Dravet syndrome.

Disclosures

Regular activities on behalf of a company: Scientific Advisory Board (UCB, Janssen-Cilag EMA); Clinical trials: as co-investigator or study contributor (UCB Australia Pty Ltd., Eisai Inc., Upsher-Smith Labs Inc., Schwarz Biosciences GmBH, Lundbeck Inc., BIAL – Portela & Ca, S.A. GlaxoSmithKline Pty Ltd.); Conferences: attendance as contributor (Athena Diagnostics, UCB, BIOCODEX, Janssen-Cilag EMA, GlaxoSmithKline).

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