

# Dravet syndrome

## Abstract

Dravet syndrome is considered one of the refractory epileptic encephalopathies, with polymorphic seizures and variable outcome which is more or less patient dependent.<sup>1</sup> It is caused by genetic alterations in *SCN1A* gene encoding the  $\alpha$ -subunit of the voltage-gated sodium channel. Various antiepileptic medications have shown efficacy in seizure control, though other antiepileptic should be avoided in this disease as they may trigger seizures.<sup>2</sup>

**Keywords:** Dravet syndrome, Myoclonic epilepsy, *SCN1A* gene

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**Abbreviations:** DS, Dravet Syndrome; SMEI, Severe Myoclonic Epilepsy of Infancy; CBD, Cannabinoid

Dravet syndrome (DS) is one of the refractory epileptic encephalopathies,<sup>3</sup> one of the spectra of severe myoclonic Epilepsy of Infancy (SMEI) which occurs in otherwise healthy individuals.<sup>2</sup> Its incidence has been estimated to be 1 in 20000- 40000. It is more common in males than in females. Positive family history is encountered in one fourth of the cases. DS Usually started by clonic/ tonic-clonic seizures, hemi-convulsions or generalized seizures. They used to have febrile seizures as an initial presentation which will be followed by afebrile seizures thereafter. Seizure frequency will vary on individual basis, though usually lies between once every one- two months. Status epilepticus is common in the form of generalized tonic clonic or hemi-clonic seizures; especially through the few months after presentation. Other forms of seizures, e.g. atypical absences, myoclonic and complex partial seizures will be elicited by the second or third year of life. Seizures will start to show increased frequency and decreased duration over time. Triggering factors like eye closure, photic stimulation can be beneficial through regular EEG recording, which is usually normal in the beginning of the disease and started to show generalized spike and polyspikes epileptiform discharges by the second year.

Dravet syndrome is characterized by psychomotor developmental slowing, cognitive deficits in addition to behavioral disorders; autistic traits and ataxia. It is caused by genetic alterations in *SCN1A* gene (2q24.3) encoding the  $\alpha$ -subunit of the voltage-gated sodium channel Nav1.1 are seen in 70–80% of patients with DS, and approximately 50% of these defects truncate the Nav1.1 protein.<sup>4</sup> The pathogenicity of *SCN1A* mutations will have its effect on the wider disease phenotype. Whole exome sequencing in *SCN1A* negative patients with Dravet syndrome identified *GABRA1* and *STXBP1* making a significant contribution to Dravet syndrome.<sup>5</sup>

Pharmacological treatment showed fair response to valproate, clobazam and stiripentol, though the use of stiripentol as an add on therapy to standard dual therapy with valproate and clobazam showed response rate up to 66.7% in recent studies with marked reduction in seizures duration and frequency. Stiripentol was well tolerated.<sup>6,7</sup>

Recent trials suggest that topiramate can be of benefit, but this may be an issue in hot countries. Phenytoin, lamotrigine, vigabatrin and carbamazepine should be better avoided due to the risk of worsening seizures. Ketogenic diet showed at least 50% seizure reduction, seizure freedom in cases of DS. This renders the ketogenic diet<sup>8</sup> as a good alternative to medication for seizure management in children with Dravet syndrome.

Selective serotonin reuptake inhibitor (fluoxetine) showed marked reduction in seizures in an adult patient with Dravet syndrome;<sup>9</sup> it is postulated that this effect is through increasing brain serotonin levels as were previously encountered with fenfluramine use. Cannabinoid, cannabidiol (CBD)<sup>10</sup> controlled studies focusing on their effect in target intractable epilepsy populations such as patients with Dravet syndromes are being planned.

Besides seizure control, patients with DS will need long term multidisciplinary rehabilitation and intervention therapy, including physiotherapy, occupational therapy and speech therapy sessions.

In a recently published study, the first successful generation of a human-based in vitro DS model has been reported. These data are consistent with a functional decline in GABAergic neurons, which may contribute to DS epileptogenesis.<sup>11</sup> These results are encouraging that patient-derived iPSC models can be utilized in human epilepsy research. They may, in fact, provide unparalleled insight into pathogenic mechanisms, and a uniquely suited research platform for drug development, which gives a real hope for these patients in the near future.

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None.

## Conflicts of interest

None.

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