

Dravet Syndrome

Also known as: DS, Severe myoclonic epilepsy of infancy (SMEI), Severe myoclonus epilepsy of infancy, Developmental and epileptic encephalopathy 6 (DEE6), Epileptic encephalopathy, early infantile 6 (EIEE6)

Overview

Dravet Syndrome (DS) is a genetic encephalopathy characterized by a drug resistant epilepsy which appears in first year of life in previously healthy children; then, a neurodevelopmental delay become evident, together with motor, language and behavioural problems. Diagnosis is made on the basis of the clinical features. In 75-85% of cases, genetic tests show a mutation in the SCN1A gene, which encodes the alpha subunit of voltage-gated sodium channel Nav1.1. Although consistent genotype-phenotype correlations have not been firmly established, truncating mutations have been associated with a worst cognitive outcome. Approximately 90 percent of mutations arise de novo; family members harboring the same mutation may be asymptomatic or mildly affected. Additional genes that have been identified as mutated in patients with a DS phenotype include PCDH19, SCN1B, GABRA1, STXB1, CHD2, SCN2A, HCN1, KCNA2, and GABRG2.

1. Incidence and Prevalence

DS affects an estimated of 1 in 15'700 to 1 in 40'000 live births. Its prevalence is unknown, and it is highly suspected to be underdiagnosed in adults. In some studies, DS accounted for 3% of cases of epilepsy among children presenting with a seizure within the first year of life, and for 2.5% of patients who had a seizure after a vaccination presenting in the first year of life.

2. Diagnosis of Dravet Syndrome

Diagnosis is made on the basis of the electro-clinical phenotype.

Genetic tests may confirm the etiology, but negativity of all genetic tests does not exclude the diagnosis.

Genetic tests should encompass research of mutations of SCN1A gene, including next generation sequencing and copy number variations. Due to the fact that several genes can be associated to DS, epilepsy comprehensive NGS panels – or even broader analysis such as whole exome sequencing (WES) or whole genome sequencing (WGS) should be performed in case of negativity of SCN1A gene studies.

3. Age of onset

The first symptom is a seizure occurring within the first year of life, usually between five and eight months, in a previously healthy child. Very rarely seizures may start in the second year of life. Typically, first seizure is a febrile convulsion, which may be either unilateral (hemiclonic) or bilateral. Precipitant factors including fever/illness, vaccination or bathing may trigger further seizures, which are often prolonged, lasting more than 10 to 15 minutes and sometimes evolving into status epilepticus.

During the second year of life, new types of seizure appear. Epilepsy is refractory and neurodevelopmental impairment become evident: children develop an unsteady gait, language progresses slowly, fine motor abilities do not develop well. Behavioral disturbances emerge during early childhood, namely attention deficit, hyperactivity, autistic traits, and relational difficulties.

4. Seizure types at presentation

Children usually show several seizure types. Seizures may be triggered by several stimuli, including fever/hyperthermia, emotional stress or excitement, flashing lights, contrasting lights and visual patterns.

Convulsive seizures

Convulsive seizures may be generalized tonic-clonic, clonic, or alternating hemiclonic. Usually a convulsive seizure is the first type of seizure that appears.

Generalized tonic-clonic seizures may be either generalized at onset or secondarily generalized, with a focal onset that may be brief and easily missed, consisting of bilateral, asymmetric, tonic contraction, leading to variable posture during the seizure. This phase may be mixed with, or immediately followed by, clonic jerking, starting by the face and involving limbs asymmetrically and asynchronously.

Hemiclonic seizures may affect either side in the same patient. This alternating pattern is characteristic of DS and may be helpful diagnostically.

Convulsive seizures may be prolonged and evolve into status epilepticus. A postictal transitory hemiparesis may remain after prolonged hemiclonic seizures.

Myoclonic seizures

Myoclonic seizures appear between the age of 1 and 5. They may be focal, involving axial muscles, at times manifesting as rhythmic movements referred to as "head nodding", or arms and shoulders; others may be massive. They may be isolated or occur in brief clusters of two or three myoclonic jerks. Myoclonic seizures may be spontaneous or triggered by photic stimulation, eye closure, variation in light intensity, or fixation on patterns.

Absence seizures

Absence seizures may appear at different ages, either between 1 and 3 years, together with myoclonic seizures, or later on, from 5 to 12 years. They may be accompanied by eyelids myoclonia or other pronounced myoclonic components. Absence status may also manifest, appearing progressively as long-lasting impairment of consciousness of variable intensity.

Focal seizures

They may appear early, from 4 months to 4 years. Focal seizures appear mainly with impaired awareness and prominent autonomic symptoms (pallor, cyanosis, rubefaction, respiratory changes, drooling, sweating). Focal seizures without impaired awareness may also be present, as versive seizures or clonic jerks limited to a limb or one hemiface.

Tonic seizures

Tonic seizures are not usual and may appear during sleep after 6 years of age.

Obtundation status

This is a special seizure type in Dravet Syndrome and consists of an impairment of consciousness, variable in intensity, with fragmentary and segmental, erratic myoclonia, of low amplitude, involving limbs and face, sometimes associated with drooling. Patient may or may not react to stimuli, according to the degree of consciousness, or perform simple activities. It may last hours or days.

5. How do seizure types change over time?

Convulsive seizures are present throughout life in all patients, while hemiclonic seizures become less common with age, and absence seizures and myoclonic seizures tend to disappear.

Temperature-sensitivity and, in general, reflex seizures usually decrease with age.

Convulsive status epilepticus are more frequent in infancy and childhood than adulthood.

6. EEG features

At onset, EEG background activity is usually normal; in some cases, a rhythmic theta activity of 4-5 Hz is noted over the rolandic and vertex areas. Background activity remains normal or slightly abnormal in 50% of cases; in the remaining cases it becomes slow and poorly organized, especially in periods of multiple seizures. When present, epileptic discharges are focal, multifocal or generalized, and there is no relationship between the site of interictal anomaly and the site of seizure

origin. Sleep activity is usually well structured. Photosensitivity has been reported as one of the main features of DS, occurring especially in patients with massive myoclonus; it is often difficult to analyse it because it does not remain constant during the course of the disease.

7. Comorbidities

DS is a Developmental and Epileptic Encephalopathy. This, developmental impairment is thought to be caused directly by the genetic mutation and not only by the epileptic activity, which may contribute in some phases to a regression or a further neurocognitive slowing. A series of comorbidities affect patients with DS, being only partially due to the seizure burden.

Cognitive impairment

Cognitive impairment is seen in almost all patients, mostly in the moderate to severe range. Regression is rare. Attention, visual motor integration, visual perception, and executive functions tend to be more impaired than language. Usually there is no further cognitive decline after the age of five to six years, and patients tend to progress slowly.

Motor impairment

Children start to walk at a normal age but then show an unsteady gait. A clear non-cerebellar ataxia is evident in most patients, leading to poor coordination, tremor and dysarthrias. With growth, a gait deterioration is seen with a typical "crouched gait" pattern, characterized by increased hip and knee flexion and ankle dorsiflexion throughout the stance phase of gait. Parkinsonian signs (bradykinesia, antecollis, camptocormia) are not infrequent in adulthood.

Language disorders

Children start to speak at a normal age, but then language progresses slowly and remain poor. A lexical poorness and frequent phonetic and phonological errors are classically present.

Behaviour and autistic traits

Behavioural issues constitute a major problem in most patient, in particular, attention deficit and hyperactivity are very often observed. Poor comprehension and poor verbal communication largely contribute to the deterioration of social relationship, especially in adolescence. Although autistic traits may be observed, only a few children are actually autistic.

Sleep and nutrition

The majority of patients with DS have sleep problems, especially sleep-wake transition disorders and difficulty in maintaining sleep. Appetite issues, avoiding/restricting food intake and eating difficulties are also often reported.

Skeletal deformity

Foot deformity, tibial torsion, hip internal rotation/femoral anteversion, scoliosis may be present.

8. Treatment

At the moment, treatment is symptomatic and aims to control seizures. Unfortunately, in almost all patients, seizures are refractory and tend to be present all life-long; however, a reduction of seizure rates relates with a better quality of life and higher daily energy, allowing child to progress.

During infancy and childhood, avoidance of specific seizure triggers may be useful, such as preventing rapid changes in body temperature or minimizing photic and visual pattern stimulations.

Once diagnosis is made, the antiseizure drug approach must exclude sodium channel blocking drugs, such as carbamazepine and its analogs (oxcarbazepine and eslicarbazepine), lamotrigine, and phenytoin, which are known to worsen the seizure rates and cognitive outcomes. Other drugs to avoid include vigabatrin, tiagabine, pregabalin and gabapentin.

Accepted first-line agents include clobazam and valproic acid, which can be associated to stiripentol. Benefit has also been noted with topiramate, levetiracetam, the ketogenic diet and vagal nerve stimulation. Fenfluramine and cannabidiol have recently shown efficacy in clinical trials.

9. Individualised emergency protocols

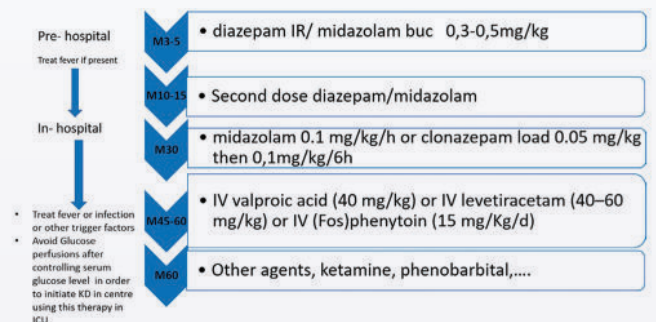


FIGURE 1 Proposed protocol for the treatment of prolonged seizures in association with Dravet syndrome. buc, buccal; ICU, intensive care unit; IR, intrarectal; IV, intravenous; KD, ketogenic diet; M, minute [Color figure can be viewed at wileyonlinelibrary.com]

10. Review the impact of seizures, drugs & comorbidities on:

- Day-to-day activities
- Overall well-being
- Mental health
- Physical health
- Independence
- Biological and psychiatric health
- Behaviour

11. Provide patient and/or carer with:

- Individualised emergency protocol
- SUDEP risk management
- Genetic counselling
- Individualised rehabilitative program
- Patient, carer & employer support requirements (neuropsychological evaluation, guidance, potential psychiatric support)

For Patient Support contact:

Dravet Syndrome European Federation

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1. How common is Dravet Syndrome?

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2. When do symptoms first appear?

The first symptom is a seizure occurring within the first year of life, usually between five and eight months. Very rarely seizures can start in the second year of life. Typically, first seizure is a febrile convulsion, which may be either unilateral (hemiclonic) or bilateral. Precipitant factors, including fever/illness, vaccination, and bathing, may trigger further seizures, which are often prolonged, lasting more than 10 to 15 minutes and sometimes evolving into status epilepticus.

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3. What are the types of seizures seen in Dravet Syndrome?

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4. Is Dravet Syndrome linked to any other epilepsy syndromes?

Epilepsies can be defined as syndromes based on the different seizure types, EEG patterns, age of onset or based on the cause, if known, as well as associated co-morbidities (see other problems below). Dravet Syndrome is an epilepsy syndrome in its own right as it has characteristic features with specific genetic causes.

5. How frequent are seizures typically in Dravet Syndrome?

Seizures may become very frequent with multiple events per day, especially absence seizures and myoclonic seizures. Convulsive and focal seizures may present in cluster, facilitated by fever or sleep.

6. How may seizures change over time?

Convulsive seizures are present throughout life in all patients, while hemiclonic seizures become less common with age and absence seizures and myoclonic seizures tend to disappear.

Temperature-sensitivity and in general reflex seizures usually decrease with age.

Convulsive status epilepticus are more frequent in infancy and childhood than adulthood.

7. What other problems apart from epilepsy, affect people with Dravet Syndrome?

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8. What are the treatment options for Dravet Syndrome?

Treatment is symptomatic and aims to seizures control. Unfortunately, in almost all patients seizures are refractory and tend to be present all life-long; however, a reduction of seizures rate relates with a better quality of life and higher daily energy.

During infancy and childhood, the avoidance of specific seizure triggers may be useful, such as preventing rapid changes in body temperature or minimizing photic and visual pattern stimulations.

Once diagnosis is put, the antiseizure drug approach must exclude sodium channel blocking drugs, such as carbamazepine and its analogs (oxcarbazepine and eslicarbazepine), lamotrigine, and phenytoin, which are known to worsen the seizures rate and cognitive outcome. Other drugs to avoid include vigabatrin, tiagabine, pregabalin and gabapentin.

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9. What is the emergency protocol for seizures?

Emergency protocol is prepared ad hoc for each patients by his/her physicians.

10. What could I ask my doctor or specialist epilepsy nurse about?

- A personalized rescue medication plan for prolonged or cluster seizures.
- The side effects of medication particularly when changing treatment
- Genetic counselling
- Liaison with school or college for support during education
- Patient, carer & employer support requirements including neuropsychological evaluation, guidance, potential psychiatric support
- An individualized habilitation plan
- Sudden Unexpected Death in Epilepsy (SUDEP) risk management



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