Dravet Syndrome

Also known as: DS, SMEI, Severe myoclonic epilepsy of infancy, Severe myoclonus epilepsy of infancy

Overview

Dravet Syndrome 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% genetic tests show a mutation of SCN1A gene, which encodes for alfa subunit of voltage-gated Sodium Channel. 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 can be asymptomatic or mildly affected. Additional genes that have been identified in patients with a DS phenotype include PCDH19, SCN1B, GABRA1, STXBP1, CHD2, SCN2A, HCN1, KCNA2, and GABRG2.

1. How common is Dravet Syndrome?

Dravet Syndrome affects an estimated 1 in 15,700 to 1 in 40,000 live births. Its prevalence is thought to be underestimated in adults.

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 pro-longed, 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 dis-turbances emerge during early childhood, namely attention deficit, hyperactivity, autistic traits, and relational difficulties.

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

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

Convulsive seizures

Convulsive seizures may be generalized tonic-clonic, clonic, and alternating hemiclonic.

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

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

Convulsive seizures may be prolonged and evolve into status epilepticus. A postictal transitory hemiparesis can residue 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 can be spontaneous or triggered by photic stimula-tion, eye closure, variation in light intensity, or fixation on patterns.

Absence seizures

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

Focal seizures

They can appear early, from 4 months to 4 years. Focal seizures are mainly with impaired awareness and prominent autonomic symptoms (pallor, cyanosis, rubefaction, respiratory changes, drooling, sweating). Focal seizures without impaired awareness can 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 age.

Obtundation status

It 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 can or cannot react to stimuli, according to the degree of consciousness, or perform simple activities. It can last hours or days.

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. Convul-sive 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 adultness.

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

Dravet Syndrome is a Developmental and Epileptic Encephalopathy. This means that developmental impairment is thought to be caused directly by the genetic mutation and not only by the epileptic activity, which can contribute in some phases to a regres-sion or a further neurocognitive slowing. A series of comorbidity affect patients with Dravet Syndrome, being only partially due to the seizure burden.

Cognitive impairment

Cognitive impairment is seen 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. After the age of five to six years, usually there is no further cognitive decline and patients tend 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, together with poor coordination, tremor and dysarthrias. With the growing, 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. Par-kinsonian signs (bradykinesia, antecollis, camtpocormia) 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 alimentation

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

Skeletal deformity

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

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 worse the seizures rate and cognitive outcome. 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 not-ed with topiramate, levetiracetam, the ketogenic diet and vagal nerve stimulation. Fenfluramine and cannabidiol have recently shown efficacy in clinical trials.

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, po-tential psychiatric support
- An individualized habilitation plan
- Sudden Unexpected Death in Epilepsy (SUDEP) risk management

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For Patient Support contact:
Dravet Syndrome European Federation
www.dravet.eu
info@dravet.eu

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