Dravet syndrome: an update

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Summary

Dravet syndrome is a severe epilepsy syndrome of infancy characterised by seizures of multiple types, often prolonged and particularly fever-sensitive, with onset in the first year of life, and subsequent developmental delay. This article aims to present updated data on this syndrome, for which complete and extensive clinical descriptions led to the discovery of a link with a major gene, SCN1A, on which abnormalities are found in at least 70% of the patients tested. Our review article follows and summarises the data published in a 2011 supplement issue of Epilepsia, entitled Severe Myoclonic Epilepsy – Dravet Syndrome: Thirty years Later.

Key words: Dravet syndrome

Introduction

Dravet syndrome is a severe epilepsy syndrome of infancy characterised by seizures of multiple types, often prolonged and particularly fever-sensitive, with onset in the first year of life, and subsequent developmental delay. This article aims to present updated data on this syndrome, for which complete and extensive clinical descriptions led to the discovery of a link with a major gene, SCN1A, on which abnormalities are found in at least 70% of the patients tested [1–4]. Our review article follows and summarises the data published in a 2011 supplement issue of Epilepsia, entitled “Severe Myoclonic Epilepsy – Dravet Syndrome: Thirty years Later” [5].

Historical considerations

Dravet syndrome was identified by Dr Charlotte Dravet in 1978 as severe myoclonic epilepsy in infancy (SMEI) [6]. Two forms were described later, according to predominant clinical features: typical SMEI and atypical or borderline SMEI (SMEB), in which myoclonic seizures are lacking and developmental delay may be milder [7–10]. Because of this clinical heterogeneity, the eponym Dravet syndrome has been preferred to SMEI (Engel, 2001). Dravet syndrome fulfils the criteria of an epileptic encephalopathy as defined by the International League Against Epilepsy (ILAE) in 2010: an “electroclinical syndrome associated with a high probability of encephalopathic features that present or worsen after the onset of epilepsy tending to be pharmacoresistant” [11, 12].

The frequency of Dravet syndrome is estimated at around 1/20 000 to 1/30 000 births [10]. In epileptic children aged less than 15 years, the rate of Dravet syndrome is 1.4% [13].

Vaccinations (especially for pertussis) have been falsely implicated as a causal factor in children with a so-called vaccine encephalopathy. Most of these children in fact had a de novo mutation on SCN1A [14] in a context of Dravet syndrome. Although vaccinations, through the febrile reaction they induce, may facilitate earlier onset of Dravet syndrome in patients with SCN1A mutations, these should not be withheld because they do not affect the outcome of the disease, and their benefits clearly outweigh the risks [15].

Clinical presentation

Seizures start during the first year of life in otherwise normal infants. The initial event is often a prolonged, apparently generalised or unilateral clonic seizure. It frequently appears in the context of a febrile disease, which may make it difficult to differentiate Dravet syndrome from a simple febrile seizure, initially. Additional nonfebrile seizure types rapidly appear, though, and repeated status epilepticus episodes, pharmacoresistance and developmental delay are the rule.

Seizure types

The various seizure types that may be observed in Dravet syndrome include:

- Convulsive seizures, such as apparently generalised clonic seizures or tonic-clonic seizures, and alternating unilateral clonic seizures: most of these are, in fact, secondarily generalised events, or so-called “unstable” seizures, shifting from one hemisphere to the other. They tend to persist throughout the patient history.

- Myoclonic seizures: these can be massive, involving all muscles and sometimes leading to a fall, or milder, involving only the axial muscles and described as “head nods”. They usually occur several times a day, either
isolated or in short bursts, without clear impairment of consciousness. Dravet syndrome has to be differentiated from myoclonic epilepsy in infancy (MEI), a rare epileptic syndrome occurring in the first two years of life in normal children, characterised by brief generalised myoclonic seizures with a good response to valproic acid, and a favourable long-term prognosis [16, 17].

- Atypical absence seizures: these are characterised by a sudden impairment of consciousness of variable intensity, and may be combined with a myoclonic component. They may be difficult to differentiate from “pure” myoclonic seizures. They occur in 40% to 93% of the cases [18].
- Focal seizures: these are focal motor seizures of a limb and/or a hemiface, with or without loss of consciousness and autonomic symptoms, which can secondarily generalise. These seizures occur in 43% to 78.6% of patients [19–21].
- Tonic seizures are exceptional in Dravet syndrome.

The occurrence rate for each seizure type is not known with precision.

All seizures are sensitive to elevated body temperature (fever, hot water immersion, intense physical exercise), and photosensitivity (noted in 40% of the patients, often during the first year of life) or pattern sensitivity are frequent [19].

Development and behaviour

The developmental phenotype spectrum is wide. In most patients, developmental delay occurs after the second year of life. Mental retardation (mostly moderate to severe) occurs in all children, and their language progresses very slowly. On the motor side, typical children start walking and talking at a normal age, but their gait remains unsteady. Neurological deterioration (motor disorders, including pyramidal or extrapyramidal signs, coordination difficulties, balance and fine motor disabilities) is often observed on follow-up.

The development is often reported as “stagnating” during the next years of life. Early prolonged seizures have not been associated with a worse developmental outcome, but the lack of early absences and myoclonic seizures seem to be associated with a better outcome. The presence or absence of SCN1A mutations has not yet been clearly correlated with a specific developmental phenotype [20].

Behavioural disorders include autistic traits, hyperactivity, and attention deficit, opposition and sleep disorders, and are often concurrent with the cognitive decline.

Cassé-Perrot et al. [21] evaluated the neuropsychological features of 20 patients over 3 years. All children with Dravet syndrome had cognitive and behavioural problems. Neuropsychological skills were all deficient, in motor, linguistic and visual aspects. Every patient had poor motor function with limited coordination skills; language expression and comprehension was problematic, with dysarthria and no fluency; all had visual-constructive and visual-spatial deficits.

EEG findings

As with seizures, a great variability exists in electroencephalographic (EEG) features. Although some seizure types may be more specific for Dravet syndrome, such as the aforementioned falsely generalised and unstable seizures, no interictal or ictal electroencephalography findings are pathognomonic. Rather, it is their progressive modification (as described below) that may suggest the diagnosis [19].

Interictal EEG

The background activity is often normal until the end of the first year of life. Theta activity, as well as brief discharges of spike waves, may appear early in the course of the disease. A steady state is often noted between two to five years, with increasing paroxysmal discharges of generalised spike waves and fast polyspike waves, and slowing of the background. Sleep recordings usually show physiological features. The background activity may remain normal in up to 40% of patients with Dravet syndrome [22].

Ictal EEG

Falsely generalised seizures may be associated with either a focal onset, bilateral asymmetric abnormalities from the onset till the offset, or bilateral discharges (such as a slow spike or a spike wave) from the onset, but becoming asymmetric later on.

Unstable seizures are characterised by alternating discharges emerging from different parts of the brain. The location of the EEG discharges may change during the same event, and the pathways of propagation are variable from one seizure to another.

Myoclonic seizures show generalised or multiple spike waves at 3 or more Hz with two or three brief bursts of extensor postural changes.

Atypical absences are associated with generalised irregular spike waves at 2–3.5 Hz.

Focal seizures usually correlate with a rhythmic sequence of fast polyspike intermixed with theta activity arising from the unilateral temporo-parieto-occipital region.

Obtundation status usually correlates with diffuse dysrhythmia of slow waves with focal and diffuse spikes [19].

Genetics

Overall, 70% to 80% of Dravet syndrome patients carry a mutation on the gene that encodes the alpha 1 subunit of the sodium channel (SCN1A) [23]. Harkin et al. showed that patients with classic Dravet syndrome more frequently carry SCN1A mutations than patients with the borderline form [24].

SCN1A is one of the most relevant epilepsy genes, and has been involved in a constantly growing number of epilepsies, in addition to Dravet syndrome, such as GEFS+, atypical Panayiotopoulos syndrome, and various types of epileptic encephalopathies, among others.
The alpha 1 subunit is involved in the activation of GABAergic interneurons in the neocortex and the hippocampus. The major mechanism of SCN1A-related epilepsies is likely to be a loss of function of these inhibitory interneurons [25, 26].

More than 500 mutations along the gene have been described in patients with Dravet syndrome [27–29]. Seventy percent are sequence mutations (40% of which are truncating, 40% missense and 20% splice-site). Most of these are de novo, and 5% to 10% are familial [1–4]. Somatic or germline mosaicism has been reported in some patients and may explain the existence of a healthy transmitting parent, which has been recently reported [29]. Exon deletions or chromosomal rearrangements of SCN1A account for around 3%. Truncating mutations are linked with an earlier age of onset of seizures [28]. No correlation between the presence of a specific mutation and seizure type has been found.

Mutations of protocadherin 19 (PCDH19) have been found in SCN1A-negative female patients with a Dravet syndrome-like phenotype, also known as “epilepsy limited to females with mental retardation” [30, 31]. One Dravet syndrome patient has been reported to carry a mutation in the gamma 2 subunit gene of the GABA-A receptor (GABRG2) [32] and another one on SCN1B [33]. One Dravet syndrome patient has been reported as harbouring mutations in both SCN1A and SCN9A, suggesting that SCN9A variant can be a “modifier-gene” for Dravet syndrome [34].

In 20% to 30% of patients, the underlying genetic defect remains unknown. Other genes are likely to be discovered in a near future with the increasing availability of continuously improving genetic techniques.

Neuroimaging

Most Dravet syndrome patients have a normal brain magnetic resonance imaging (MRI). Nonspecific structural abnormalities may be observed in some children. These include diffuse cerebral or cerebellar atrophy, increased white matter signal, ventricular abnormalities, cortical dysplasia or arachnoid cysts [5]. In a few patients, cortical-subcortical atrophy developed over the years [35]. Two systematic retrospective studies have investigated MRI findings in Dravet syndrome patients [36, 37]. Siegler et al. [36] found hippocampal sclerosis in 10 of 14 children with Dravet syndrome (nine unilateral, one bilateral) after eight years of follow-up: six of these ten had an initial normal MRI, and none of them had mesial temporal lobe epilepsy. The authors concluded that prolonged febrile convulsions may be responsible for hippocampal sclerosis, but that additional factors (genetic, developmental and individual sensitivity) are also likely to play a role in the process. Striano et al. [37] analysed 58 Dravet syndrome patients and found that 13 patients (22.4%) had MRI anomalies: eight had cortical brain atrophy (ventricular abnormalities in three, cerebellar atrophy in one and hyperintense white matter signal in one), three showed ventricular enlargement only, one had unilateral hippocampal sclerosis, and one had focal cortical dysplasia. Only one patient had hippocampal sclerosis, which led the authors to conclude that an association between prolonged febrile seizures and hippocampal sclerosis is unlikely in Dravet syndrome. The origin of these structural focal abnormalities remains uncertain. No correlation has been found between MRI abnormalities and epilepsy severity. Single-photon emission computed tomography (SPECT) or positron emission tomography (PET) studies showed unilateral or bilateral hyperperfusion or hypometabolism, but without strict correlation with EEG findings.

Pharmacological treatment

Seizures in Dravet syndrome are invariably difficult to control. The combination of stiripentol, valproate and clobazam was demonstrated to be particularly effective in two randomised controlled trials [38]. Compared with placebo, a 70% reduction in seizure frequency was reported [38]. This combination also seems to reduce the duration of seizures.

It is currently recommended to start stiripentol as soon as the diagnosis of Dravet syndrome is secure. Stiripentol is a GABAergic agent that acts as a modulator of the GABA-A receptor via its alpha 3 subunit [39]. Stiripentol is also an inhibitor of cytochrome P450 with potential increase in plasma concentration of other antiepileptic drugs, whose dosage should be reduced accordingly. Side effects include drowsiness, slowing of mental function, ataxia, diplopia, loss of appetite, weight loss, abdominal pain and neutropenia, but overall, stiripentol has a good long-term safety profile. Topiramate, levetiracetam and bromide may be efficient as adjunctive therapies. A favourable effect of add-on fenfluramine has also been recently reported (ICNA congress, Brisbane, 2012).

Lamotrigine, carbamazepine, vigabatrin and phenobarbital may worsen seizures and should be avoided in Dravet syndrome patients.

Nonpharmacological treatments

The ketogenic diet

The ketogenic diet (KD) is a valuable addition or alternative to medication in Dravet syndrome. In a recent study [40] of 16 patients with Dravet syndrome, two were seizure-free, ten had a 75% to 99% decrease and four a 50% to 74% decrease in seizures, after a minimum two years of follow-up. Caraballo et al. [41] showed that most of their Dravet syndrome patients treated with a KD for at least one year had a decrease of more than 75% in their seizures, that all had a better quality of life and that all had a reduction in the number of antiepileptic drugs required. The reported favourable effects on seizure control and on EEG features seem to be long-lasting, even after the diet has been discontinued. The classical diet is based on a 4:1 ratio of fat to carbohydrates and protein (90% of the energy comes from fat and 10% from carbohydrates and protein). It mimics the biochemical response to starvation and ketone bodies become the main source of energy for the brain. Alternative diets, such as the Atkins diet and the low-glycaemic index diet seem to be as...
efficient as the classic KD [42]. Expert recommendations on the use of the KD have been published [43]. Because several inborn errors of metabolism are absolute contraindications for the KD, these should be ruled out before starting the diet. Patients on a KD should be supplemented with sugar-free multivitamin products. Counselling and frequent follow-up visits with paediatric neurologists and nutritionists, as well as biological parameter monitoring are needed. Its long-term safety profile is favourable. In a recent study which analysed the effects of the KD after more than six years of follow-up [44], rare complications, such as kidney stones, decreased growth and bone fractures, were reported, but lipid profiles were not significantly affected.

Vagus nerve stimulation

Vagus nerve stimulation (VNS) may be an alternative treatment, but further studies in Dravet syndrome are needed as only rare patients have benefited from this approach. Three Dravet syndrome patients were reported by Cersosimo et al. [45]: two of them had a 50% to 74% decrease in seizure frequency, one remained unchanged. The efficacy progressively improved with treatment durations of up to 36 months. No significant complications were reported, except transient local pain and voice hoarseness.

Outcome in adulthood and mortality

A few patients were followed up until adulthood [22]. Moderate to severe mental retardation and impairment of communication skills were observed in all of them. Motor abnormalities often include cerebellar features affecting gross and fine movements. Owing to orthopaedic problems, such as kyphoscoliosis, flat or claw feet, walking is often difficult. In some patients, a major personality disorder, with autistic or psychotic features, has been observed. Patients who live independently are the exception. The social outcome is poor, as well. Epileptic seizures become less frequent and nocturnal generalised tonic-clonic seizures with a focal onset are the most frequently observed. Fever, photo- and pattern sensitivity decreases with age [46].

A high risk of mortality exists in Dravet syndrome, particularly during childhood. Major causes of death include complications of status epilepticus in younger children, and sudden unexpected death in epilepsy (SUDEP) in older ones. The minimum SUDEP rate is estimated at 15.4% [22, 35].

Future perspectives

Dravet syndrome should be suspected in any healthy child with prolonged and recurrent convulsions triggered by fever or hyperthermia in the first year of life, particularly if the evolution shows a polymorphic pharmacoresistant epilepsy with psychomotor delay. The presence of SCN1A abnormalities is an additional diagnostic argument, and genetic analyses should be rapidly performed in order to optimise management and treatment approaches. The role of additional genes such as SCN9A modifying SCN1A requires more studies, and a precise phenotype-genotype correlation remains to be established. Most cerebral MRI of Dravet syndrome patients are normal, but some develop atrophy or hippocampal sclerosis on follow-up. The origin of these structural abnormalities remains unclear. No correlation seems to exist between the presence of MRI abnormalities and the duration or severity of epilepsy. Structural changes may themselves become a substrate for the development of encephalopathic features. Recently developed imaging tools such as simultaneous recording of electroencephalography and functional magnetic resonance (EEG-IMRI), spectroscopy or diffusion tensor imaging (DTI), may help characterise this syndrome. In a recent study, Moehring et al. tried to identify a specific epileptic network in ten patients with SCN1APositive Dravet syndrome using EEG-IMRI; no common activation pattern was observed in the nine children in whom blood oxygen dependent level signal changes were identified [47].

The reasons for cognitive decline is not yet elucidated, either. The question whether Dravet syndrome is a true epileptic encephalopathy or not remains open. Inherent to the concept of epileptic encephalopathy is the notion that suppression of epileptic seizures may improve development. Recent observations show that less severe cognitive and behavioural disorders may occur if the diagnosis is made early in the course of the condition and if adequate drug therapy is used [48].

In conclusion, long-term prospective studies are needed to establish whether earlier diagnosis, adequate treatment and better seizure control may influence the progress of the clinical deterioration observed in this severe condition.

References