REVIEW

Dravet syndrome

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Purpose of review

This review will illustrate the electroclinical description of Dravet syndrome, highlighting the difficulty to understand the correlation between the SCN1A mutation and clinical characteristics, including the frequent comorbidities. Therefore, the efficacy of the new treatment options, which now become available, should not only focus on seizure frequency reduction but also on the long-term effects on these comorbidities, such as intellectual disability, motor and sleep problems.

Recent findings

Comprehensive guidelines for a more standardized treatment in children with Dravet syndrome have been published. First-line and second-line treatments actually include only a few antiseizure medications, such as valproate, clobazam, stiripentol, topiramate and bromide. Cannabidiol and fenfluramine were shown to be very effective drugs and will become standard second-line drugs in Dravet syndrome. There are preliminary data showing that both drugs also have a positive effect on quality of life and on cognitive functioning. Genetic treatments in Dravet syndrome most likely will dramatically change the natural course of this refractory epilepsy syndrome.

Summary

A better understanding of the full clinical picture is necessary to understand the potential value of new treatment options in Dravet syndrome. Treatment nowadays with the newer drugs becomes much more standardized and effective, and this will have a positive effect on long-term overall outcome.

Keywords

cannabidiol, Dravet syndrome, epileptic encephalopathy, fenfluramine, *SCN1A*

INTRODUCTION

In 1978, Charlotte Dravet described a group of children with difficult-to-treat early-onset epilepsy. Myoclonic seizures were a typical seizure type in these patients but they suffered from different seizure types and all had a moderate-to-severe intellectual disability. To differentiate from Lennox Gastaut epilepsy, she called this syndrome ‘severe myoclonic epilepsy of infancy’ (SMEI) [1]. Very soon, the typical phenotype was also recognized by other groups. Later on, this epilepsy syndrome was called ‘Dravet syndrome’ [2]. In 2001, the cause of Dravet syndrome was discovered: In more than 85% of the very typical Dravet syndrome patients, a mutation in the *SCN1A* gene was found [3]. This was actually one of the first genetic breakthroughs in epilepsy, correlating a typing electroclinical epilepsy syndrome with a de novo genetic mutation.

As already described by Dravet, this syndrome is very drug-resistant and is a prototype of what is now called a ‘developmental encephalopathy with epilepsy’. Children with Dravet syndrome suffer from many associated problems. Almost all develop a moderate-to-severe intellectual disability. Motor, behavioral and sleep problems are also observed frequently [4,5]. There is an ongoing debate to understand what the contributing roles are of the SCN1A mutation and/or seizure frequency (e.g. early life seizures, or number of status epilepticus) on the severity of these comorbidities [6▪]. In addition, there is a higher risk for sudden unexpected death in epilepsy (SUDEP) in Dravet syndrome than in other childhood epilepsy syndromes [7]. Luckily, in recent years, new antiseizure medications (ASM) became available to treat these children. There is justified hope that genetic therapies soon will be available too. In this short review, newer insights with a focus on newer treatment options will be discussed.

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KEY POINTS

- Dravet syndrome is the prototype of a developmental and epileptic encephalopathy.
- Difficult to understand interactions between epilepsy and gene mutation explain the severe comorbidities seen in Dravet syndrome.
- In recent years, more efficacious antiseizure medications have been developed for Dravet syndrome, including cannabidiol and fenfluramine.

CAUSE

In 2001, Claes *et al.* described a de novo mutation in the *SCN1A* gene in seven children with a typical Dravet syndrome phenotype [3]. First convulsive seizure was observed between 2 and 6 months and was associated with fever in 4/7. All children developed drug-resistant epilepsy and intellectual disability. Many studies have confirmed that in the large majority of Dravet syndrome, a de novo mutation in *SCN1A* can be found. Although this is a 'de novo' mutation, genetic counseling and genetic examination of the parents is advised as parental mosaicism is possible and cases of 'familial Dravet syndrome' have been described [8]. Different types of mutations are possible and to some extent genotype–phenotype correlations are possible. Truncating mutations are associated with a more severe phenotype than missense mutations, although this is not always clear at the individual level [9,10]. Not all mutations in *SCN1A* cause Dravet syndrome. There is actually a broad spectrum of *SCN1A*-associated epilepsies. This ranges from 'benign' and familial febrile seizures (GEFS+ phenotype) to an early (and often fatal) infantile epileptic encephalopathy with p.Thr226Met mutation [11–13,14▪]. Also nonepilepsy-related diseases can be associated with a SCN1A mutation, such as familial hemiplegic migraine. In a minority, mutations are found in other genes, but careful examination of these phenotypes shows that most of these patients do not have a typical 'core' Dravet syndrome. These genes include *SCN2A, SCN8A, SCN9A, SCN1B, PCDH19, GABRA1, GABRG2, STXBP1, HCN1, CHD2*, and *KCNA2* [11].

ELECTROCLINICAL DESCRIPTION

In 2011, Charlotte Dravet reviewed the characteristics in children with Dravet syndrome [15].

Typically, the first seizure occurs in infancy between 2–3 months and 16 months. In the large majority, the first seizure is seen below the age of 1 year. At that time, the development of the child is still normal, although subtle developmental difficulties can be observed in some infants. The first seizure commonly occurs in a feverish episode (sometimes after a vaccination), and in a way can be classified as an atypical febrile seizure because of the long duration and/or unilateral clonic semiology. However, generalized and shorter convulsive seizures are also possible in these early phases. After two of these prolonged seizures, the diagnosis of Dravet syndrome usually is suspected. Some of the infants already show myoclonic seizures, although these typically occur somewhat later between the ages of 1 and 2 years. Photosensitivity is a common finding and can induce myoclonic seizures. During the first and second year, it becomes clear that the development is slowing down and that developmental milestones are not reached in time. Especially language development is delayed in the most typical cases. After a long-lasting seizure, some of the children can be ataxic for several days, not related to the use of rescue benzodiazepines. Seizures remain very sensitive to temperature increases. Not only fever is a known trigger but also high outdoor temperatures or hot water. Later on, starting between 1 and 2 years, seizures occur without fever. Most commonly, these are still convulsive (long-lasting) tonicoclonic seizures and/or myoclonic seizures. Parents also report long lasting absence-like seizures, sometimes called 'obtundation status'. Focal seizures are very rare in toddlers but can become more frequent in older children. At that point, antiseizure medication has already been started and although seizure freedom is rarely obtained, medication can help to decrease the number of seizures and especially the duration of the long-lasting seizures or status epilepticus. In many toddlers and young children, a sort of pseudostationary period is reached with a fragile balance between seizure frequency, quality of life and treatment. With age, the myoclonic seizures and the absences are seen less frequently, but the (tonico)-clonic seizures remain [16]. In a Japanese study [17], it was shown that 'generalized tonic–clonic seizures', did not decrease with age, in contrast to myoclonic and atypical absence seizures. In that study, the overall seizure frequency decreased to some extent but very few patients became seizure-free. This was also confirmed in a large retrospective survey in 574 Dravet syndrome patients [5]. Overall, in that study, only 9.4% was seizure free in the last 3 months. In the infant group, this was only 3%. The adolescent and adult group did somewhat better with 14 and 11%, respectively, indicating that only few adults are satisfactorily controlled. This is also reflected by the high number of emergency admissions: Still up

to 30% of the adults needed an emergency hospital admission in the last year. This was between 60 and 80% in infants and preschool children.

Below the age of 2 years, the (interictal) EEG can remain normal, although more detailed analysis already shows some slowing of the background rhythm. Later this becomes a common finding: an overall slower background, with a dominant posterior rhythm of less than 8 Hz. Early in life, photosensitivity can be clearly demonstrated, and therefore, enough effort has to be made to test photosensitivity in early EEGs. In many children, photic stimulation during the EEG will generate myoclonic seizures [18]. This finding in a child presenting with an atypical febrile seizure actually can help to start diagnostic screening for Dravet syndrome. With age, this photosensitivity tends to diminish or disappear. Pattern photosensitivity, whenever tested adequately, remains positive in many Dravet syndrome patients. Above the age of 2 years, interictal epileptic discharges are seen on the EEG. Patterns of EEG abnormalities can fluctuate with rare to very frequent multifocal discharges or generalized epileptic discharges [19]. As for many childhood epilepsy syndromes, there is a poor correlation between interictal EEG findings, seizure frequency and response to antiseizure drug initiation. Ictal findings are typical generalized discharges, with the well known EEG patterns seen in myoclonic, tonic and clonic seizures. During an obtundation status, ictal rhythmic delta and theta activity is seen, especially in the frontal regions, and is reminiscent of the slow spike waves pattern seen in Lennox Gastaut epilepsy.

COMORBIDITIES

Overall, quality of life (QoL) is lower in children with Dravet syndrome than in normal children or in children with more benign forms of epilepsy. In a study of Brunklaus *et al.* [20], it was shown that for all items on the QoL scale, scores were about 50% lower than in the control group. This was also seen in the DISCUSS study using the EQ5D-L instrument [5]. In the study of Villas *et al.*, the most important reasons for concerns were identified. Most parents of children with Dravet syndrome are worried about cognitive, language and behavioural problems. Risk of SUDEP and worries about long-term care plans for their child were high on the list as well [4]. Brunklaus *et al.* [21] showed that above the age of 15 years, more than 80% of the Dravet syndrome patients have severe or profound learning disability. In the study of Lagae *et al.*, intellectual disability in the adolescent and adult groups was seen in more than 95%. Speech impairment was observed in more than 65% of all children, with 14.9% of children who did not talk at all [5]. A recent study showed that overall outcome actually did not correlate very well with the epilepsy history, although later onset of the seizures (>6 months) and no/few myoclonic seizures predicted a somewhat better intellectual outcome [21]. The same findings were observed for behavioural problems. With increasing age, more behavioural problems are observed in the large majority of the patients. In the study of Brunklaus *et al.* [22], more than 60% of the children above the age of 12 years were known with behavioural problems. Autistic features were studied separately and more than 50% showed some autistic traits above the age of 12 years.

Sleep problems were underrecognized for many years, but recent specialized sleep studies do show a disturbed sleep patterns in many Dravet syndrome patients, independent of seizure frequency. Not only initiation and maintaining of sleep, but also arousal and sleep transition problems are frequently observed, all possibly leading to more daytime sleepiness and drowsiness [23,24].

In recent years, many studies focused on the associated motor problems seen in Dravet syndrome. Follow-up studies into adulthood and gait analysis studies in Dravet syndrome made it clear that a rather specific motor dysfunction evolves in patients with this syndrome [25▪,26]. In early life, a fluctuating ataxic gait pattern is seen, often in a postictal phase after a long-lasting seizure. Later on, a crouch gait develops in many patients, with flexion of the hips and knees in standing position. Also, flexion of the head is often observed. Pyramidal signs can develop. In adulthood, many patients are becoming wheelchair-bound and show Parkinsonian symptoms, such as bradykinesia, rigidity and postural instability. However, the typical Parkinsonian resting tremor is not often observed in Dravet syndrome patients [27].

Patients with Dravet syndrome have a much higher risk for premature death [28]. Causes of mortality in Dravet syndrome include most commonly status epilepticus, accidents (drowning) and SUDEP. In the study of Cooper *et al.* [7], the SUDEP rate per 1000 person-years in a large cohort was 9.32, which is almost twice as high as in adult refractory epilepsy. Mortality and SUDEP in Dravet syndrome is higher in children/adolescents than in adults.

TREATMENT

At this moment, treatment in Dravet syndrome is purely symptomatic, aiming to reduce seizure frequency or at least to reduce the severity of seizures. Dravet syndrome is a notoriously difficult to treat

epilepsy syndrome and is one of the most drug-resistant epilepsies. Evidence-based treatment is difficult as only few high-level randomized controlled trials (RCT) are available: at this moment RCTs are published only for stiripentol, cannabidiol and fenfluramine [29,30,31▪,32]. Guidelines for treatment were published by a North American consensus panel and more recently by an European expert group [33,34▪].

Already after the first seizure, many clinicians will consider to start ASM, especially when this first seizure was a prolonged convulsive seizure. At that point, in both published guidelines, valproate is proposed as a first-line drug. If there are concerns to use valproate in very young children, clobazam is an alternative option in the American guidelines. Many first seizures in Dravet syndrome are hemiconvulsive, and therefore it seems logic that ASM against focal seizures (such as carbamazepine, oxcarbazepine) are sometimes considered, especially when the clinical diagnosis of Dravet syndrome is not yet clear. However, the choice for sodium channel blockers is contraindicated. Prolonged use of contraindicated drugs not only can increase the number of seizures but also is associated with a worse cognitive outcome [35]. The first-line treatment can decrease the number of seizures and the severity (duration) of the subsequent seizures but rarely the child will become seizure-free. The exact timing to introduce a second-line treatment is a challenge but typically this happens already after 3–6 months and in some children even earlier. Traditional second-line choices according to the guidelines include stiripentol (with or without clobazam), topiramate and ketogenic diet. The more recent European guidelines now also include cannabidiol (CBD) and fenfluramine as possible second-line treatment.

Already in 2000, Chiron *et al.* published a RCT on the use of stiripentol (in association with valproate and clobazam) in Dravet syndrome. There was a highly significant decrease of seizure frequency in the treated group. These findings were confirmed in later studies, and stiripentol has become a valid second-line treatment option. The use of stiripentol does require specialized management, as interactions between stiripentol and clobazam are possible because of the inhibiting effect of stiripentol on clobazam. In clinical practice, we often see that the number of long-lasting seizures/status epilepticus reduces after the introduction of stiripentol but rarely patients become completely seizure-free. Alternative second-line approaches include topiramate, ketogenic diet and bromide. Several studies reported beneficial effects of these treatments, although no RCTs are available [36–39].

A retrospective Japanese study [40] looked at the use and efficacy of the classic ASM in Dravet syndrome. Valproate was the most commonly prescribed drug and about 50% of the children had a more than 50% seizure frequency reduction at some point during the treatment period. Also for topiramate, clobazam and clonazepam about 40–50% reduction was seen. Very few children became seizure free. Of interest, best results were seen with bromide, an older and forgotten antiseizure medication [41]. In the study of Brunklaus *et al.*, similar findings were seen: the top five drugs that did yield a reduced seizure frequency were valproate (51% of patients), clobazam/clonazepam (34%), topiramate (28%), levetiracetam (13%) and stiripentol (13%). In that study, it was also clearly shown that carbamazepine and lamotrigine did increase seizure frequency in 60 and 43%, respectively [22]. Another alternative treatment option is the use of Vagus Nerve Stimulation therapy. Again, very few Dravet syndrome patients will become seizure-free but many will get benefit from this nonpharmacological treatment option. In a review article, Dibué-Adjei *et al.* [42] showed that the number of 50% responders varies between 30% and as high as 100%.

In recent years, two new antiseizure medications became available for the treatment of Dravet syndrome, following successful RCTs: cannabidiol and fenfluramine [30,31▪,32]. Cannabidiol made its way very fast into the treatment flowcharts for many epilepsies and seizure types. In an open label study with add-on CBD in children with drug-resistant epilepsy, 32 children with Dravet syndrome were included [43]. In this subgroup, a significant reduction of all seizure types was observed, ranging from 47% for clonic seizures to 83% for nonmotor focal seizures. Post hoc analysis showed that the concomitant use of clobazam was an independent predictor of seizure frequency reduction. Following this successful open-label study, the placebo-controlled RCT confirmed a statistically significant decrease of seizures with add-on cannabidiol in Dravet syndrome [30]. Median percentage reduction was 41% in the maintenance period of the study (compared with 16% decrease in the placebo group). A long-term open-label study confirmed a sustained effect in most patients [44]. Clinicians have to be aware of the potential (reversible) liver toxicity and the interaction with clobazam, necessitating a reduction of the clobazam dosage in many patients to avoid excessive drowsiness [45].

Fenfluramine is a typical example of a repurposed drug. Initially this serotonergic drug was prescribed as an antiobesity drug and withdrawn from the market in 1997 because of possible cardiac valvulopathy when used in high dosages and in

combination with phentermine [46]. Older reports did show an effect in photosensitive epilepsy, one of the characteristics in Dravet syndrome [47]. Initial noncontrolled studies showed an unexpected high rate of long-term seizure freedom in some Dravet syndrome patients [48]. Now, two RCTs confirm that fenfluramine substantially reduces seizure frequency in Dravet syndrome [31▪,32]. In a first RCT [31▪], 70% of the included patients were 50% responders at the dose of 0.7 mg/kg/day (compared with 7.5% in the placebo group). Forty-five percent of the patients were 75% responders. In the second RCT [32], with stiripentol as one of the concomitant medications, similar findings were obtained. Because of the possible interaction with stiripentol, lower dosages were used. At 0.5 mg/kg/day, 53,5% were responders (versus 6.8% in the placebo group). During these pivotal trials and also in the open-label long-term extension study, no valvular or other cardiac problems were observed. Although not a primary outcome, it was also shown in the first fenfluramine study [31▪], that QoL, and executive functioning [as measured with the Behavioural Rating Inventory of Executive Functions (BRIEF)] significantly improved, indicating that reducing seizure frequency, even during the short study period, can have a positive effect of cognitive functioning and overall well being. It is anticipated that both CBD and fenfluramine will become second-line treatments in the treatment flowchart of Dravet syndrome, as already mentioned in the European guidelines [34▪]. It remains to be seen whether an earlier start of these newer drugs will yield a better overall outcome, beyond seizure frequency reduction only. Also in this respect, more studies in children below the age of 2 years are needed to understand this better.

There are newer treatment options in the pipeline. Soticlestat is a new drug, regulating glutamate metabolism through inhibition of cholesterol 24-hydroxylase. A recent phase 2 RCT in Dravet syndrome showed a 33.8% reduction of convulsive seizure frequency (compared with a 7% increase in the placebo group; https://www.takeda.com/newsroom/newsreleases/2020/phase-2-elektra-study-of-soticlestat-tak-935ov935-meets-primary-endpoint-reducing-seizure-frequency-in-children-with-dravet-syndrome-or-lennox-gastaut-syndrome/). Larger phase 3 studies are being set up to confirm these findings.

Most likely, and following the successful strategy in neuromuscular diseases, genetic treatment will become available for Dravet syndrome as well. This remains challenging as the *SCN1A* gene is very large, and typical vector-based therapies might, therefore, be difficult. Another promising genetic approach is to boost the expression of the healthy allele of haplo-insufficient *SCN1A* gene. A study is currently being performed using antisense oligonucleotides (ASO) to increase the concentration of productive mRNA and the concentration of protein levels (sodium channel) (http://www.draccon.com/dracaena-report/2020/9/13/gene-therapy-for-dravet-syndrome-2020-update). If these techniques become clinically available, one of the crucial questions will be when these therapies are best given to a patient with Dravet syndrome. No doubt the earlier, the better, but then early recognition of a Dravet phenotype becomes even more important. In view of the still ill-understood genotype–phenotype correlation, this is not obvious so far.

CONCLUSION

Dravet syndrome is a rather homogeneous developmental and epileptic encephalopathy with a well defined genetic cause in the large majority of cases. Genotype–phenotype correlations remain challenging and it is still not completely clear how the frequent and severe comorbidities can be explained by the *SCN1A* mutation and/or severity of the epilepsy. Newer antiseizure medications, such as CBD or fenfluramine give hope to the patients with Dravet syndrome. Now, upcoming genetic therapies are awaited, which undoubtedly will change profoundly the natural course of this severe epilepsy syndrome.

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Conflicts of interest

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