Dravet syndrome, what is new?

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ABSTRACT

Dravet syndrome (DS) is one of the most severe genetic epilepsies of childhood. Charlotte Dravet described severe myoclonic epilepsy in infancy in 1978. Shortly after the initial report, many cases were published. Most of the cases have the SCN1A mutation. A variant of DS called borderline severe myoclonic epilepsy in infancy has similar clinical and electrographic features without myoclonus. The prevalence of DS is 3-6% of epilepsy cases in infancy, and the incidence is less than one per 40,000 infants. Also, there is a rare mutation in the GABARG2 and SCN1B genes. Usually, affected patients have normal developmental milestones during infancy. Then after 1-4 years of age, they start to develop refractory mixed seizure types (tonic seizures are exceptional) and psychomotor retardation, ataxia, and hyperkinesias. The EEG reveals focal or multifocal epileptic discharges and it commonly shows photosensitivity. The treatment of the seizures is challenging. The combination of stiripentol, valproic acid, clobazam, and topiramate is promising.

Historical introduction. Severe myoclonic epilepsy in infancy (SMEI) was first described in 1978 by Charlotte Dravet at Marseille, and it was briefly reported in a French medical journal.1 Soon afterward, it was recognized in Italy by Bernardo Dalla Bernardina and they together presented the first 42 cases diagnosed in Marseille at the International Epilepsy Congress in Kyoto in 1981.2 It became subsequently obvious that some patients exhibited overlapping characteristics, with the exception of myoclonic seizures, which led to the subdivision of typical and atypical, or borderline (SMEIB) forms, without an obvious difference in the prognosis. For this reason, and because this form of epilepsy was not limited to infancy, the name was changed to the eponym Dravet syndrome (DS) (Commission on Classification and Terminology of the International League Against Epilepsy [ILAE], 1989). It starts in the first year of life with febrile seizures (FS) in an, otherwise, normal infant. The FS usually are atypical. This is followed by refractory and mixed type of seizures. The most common seizure types are myoclonic, atypical absence, and focal seizures. Later on, the infant develops regression in his developmental and cognitive functions, and he begins to have behavioral difficulties. Various degrees of variability are seen in the symptoms of patient with DS; namely, they might not have myoclonic seizures.3-5 In addition, they may have characteristics in the EEG that vary from one patient to another, and on the other hand they may carry the same prognosis as patients with myoclonic seizures. These patients are classified as the borderline form (SMEIB). It is considered as one of the channelopathies after finding the mutation of SCN1A in affected patients with DS.6 It is still not clear if there are different forms of one
disease, which may carry various mutations, and also it is not known whether there is any relationship between epilepsy and psychomotor development in these patients. According to the ILAE, the DS is considered as an “epileptic encephalopathy,” defined as a disease in which there is progressive cognitive dysfunction caused by epileptic discharges. It is yet not known whether the cognitive delay noted early in the disease is considered to be an early stage of the disease.

**Definition.** The ILAE classification, typical form of DS, is defined by a refractory and mixed seizure disorder (most commonly myoclonus, atypical absence, and partial seizures) which starts after different types of febrile and afebrile seizures in an, otherwise, healthy infant. In the second year of life, the child develops cognitive and behavioral difficulties.

**Severe myoclonic epilepsy in infancy (Dravet syndrome) 30 years later.** Thirty years after its first description, DS is considered as a model of channelopathy that raises wide interest in the scientific and medical community. However, clinical and experimental implications related to the syndrome spectrum have a much wider meaning than was originally foreseen in SMEI. The animal models of the syndrome that have been developed are convincing and have already provided important insights on the mechanisms of epileptogenesis. Additional insights are emerging on the gait disorder that may accompany the clinical syndrome and, hopefully, on the mechanisms underlying cognitive impairment. There are encouraging progresses in treatment as new molecules have emerged that allow a better control of seizures and that decrease the episodes of status epilepticus (SE) in a significant proportion of patients. Unfortunately, seizure freedom remains an exception. Early mortality, often due to sudden unexpected death in epilepsy (SUDEP), is a big concern, but has been seldom studied.

**Epidemiology.** Severe myoclonic epilepsy of infancy is an uncommon disorder with an incidence of one per 2,000 to one per 40,000 children, and a prevalence of 6% of epilepsies starting below 3 years of age. Despite the increased recognition of DS, it is still considered to be rare, especially below 15 years of age where it is as low as 1.4%. A strong family history of epilepsy or FS was seen, which is variable from approximately 25-71%. In many studies, the relationship with genetic abnormalities was not investigated. The mutation found in genetic analysis is variable from 27% in patients with an SCN1A mutation, to 62.5% that demonstrate no mutation.

**SDravet syndrome.** Early on, the SCN1A mutation was found in patients with FS plus (GEFS+). Currently, more than 500 mutations have been found associated with DS and they are randomly distributed along the gene. Various mutations are found in patients with DS, 70% of cases have sequencing mutation, 40% have missense mutation, 40% have spliced-site changes, and 5-10% of cases are familial mutation, which is commonly missense in nature. An important genetic counseling issue is that several families have been reported with more than one child with DS. However, mosaicism might be found in approximately 7% of families with DS. A patient with similar clinical features of DS who tested negative for the SCN1A mutation can have SCN1A exonic deletion or chromosomal rearrangements, which involve the contiguous gene and SCN1A. This type of mutation is seen in 2-3% of all DS cases and 12.5% of patients with DS with negative mutation.

**Associated pathology.** Dravet syndrome is rarely associated with other disorders, for example, Rud syndrome, neurofibromatosis type 1, congenital heart disease, growth hormone deficiency, and hemophilia. The onset of DS is usually in the first year of life. It starts with atypical FS, but they may have seizures, which may be related to vaccination, or it may not be related to fever. All authors indicate an age at onset between 2 and 12 months, and rarely after the age of one year. The febrile convulsive seizures can be variable occurring in 28-68%. In one series, these afebrile seizures usually occurred in the context of a vaccination or of an infectious episode, or after a bath, and later on, they were associated with FS. In 25-49% of children with DS, the seizures are prolonged and it may or may not be related to fever. The first seizures can be focal. In some patients, isolated episodes of focal myoclonic jerking are noted by the parents either some weeks or some days before the appearance of the first convulsive seizure. The myoclonic jerks may start in the hours before the convulsive seizure, and it may be associated with hyperthermia. Shortly after the first FS (2 weeks to 2 months), other FS occur and afebrile seizures also appear. The child with DS develops mixed seizure types and starts to show features of psychomotor delay and then reaches a steady state between age one and 4 years. These seizure types are variable, mixed, and resistant to antiepileptic drugs such as erratic or massive myoclonic seizures, atypical absences, generalized tonic-clonic or uni-or bilateral clonic seizures, and focal seizures with or without secondary generalization. Episodes of obtundation or nonconvulsive SE with or without
erratic myoclonus is commonly noted. To differentiate it from Lennox-Gastaut syndrome (LGS), tonic seizures are very uncommon, in addition to typical EEG features.

A) Myoclonic seizures. Myoclonic seizures are considered as one of the defining features of DS. However, patients with DS appear not to present any myoclonic seizures.\textsuperscript{4,25} Such cases have been grouped as “borderline cases of SMEI” (SMEIB). Massive myoclonias have been reported for 77% of patients,\textsuperscript{4} and erratic myoclonias for about one-third of patients studied;\textsuperscript{2,3} some patients may experience both massive and erratic myoclonia.\textsuperscript{4} Myoclonic seizures are variable and usually involve the axial muscles and cause drop attacks if severe or head, shoulder, and trunk jerks when mild. They occur commonly in the minutes before the convulsion upon awakening from sleep. They are provoked by subtle light intensity,\textsuperscript{4} or more intense or continuous stimulation.\textsuperscript{2} Interestingly in approximately 25% of patients, seizures can be triggered either by interfering with a light source or observing patterns.\textsuperscript{4,26,27} The majority of massive myoclonias were associated with bursts of irregular spike-waves or polyspike-waves.\textsuperscript{4} This has been observed in half of the individuals studied by Doose et al,\textsuperscript{28} it was less commonly observed by others.\textsuperscript{3} Myoclonic seizures can be erratic or segmental, which may involve the distal part of the face and limbs and result in muscle twitch. Movement enhances erratic myoclonias, and they are particularly common during periods of severe and frequent convulsions; however, they also occur at rest. The seizures are seldom intense, and may be more palpable than visible; however, imbalance and disturbances of fine coordination may occur. Interestingly, there might not be associated EEG changes associated with erratic myoclonias, which is not the case in massive myoclonias.

B) Atypical absences. Approximately 40-90% of children with DS have atypical absence.\textsuperscript{3,4,25} These appear as absence seizures with myoclonic jerks of the upper limbs, a simple fall of the head, or drop attacks. The EEG recordings identify brief discharges or irregular spike-waves. Typically during the atypical absences, which are usually prolonged and it may lasts hours or days, these patients have variable degrees of obtundation, and ataxia.\textsuperscript{2,4}

C) Convulsive seizures. The convulsive seizures can be focal or generalized at any time of the diagnosis. Most of the seizures appear to be focal with rapid secondary generalization and not generalized in onset as demonstrated by video-EEG recording in patients with DS. Interestingly, the seizures are hemiconic ones that evolve to status as noted in young children.\textsuperscript{29} These seizures tend to become briefer and it alternates from one side to another as the patient becomes older. It is commonly associated with Todd’s paralysis and asymmetric EEG features.

D) Focal seizures. More than 50% of children with DS have focal seizures, which may or may not secondarily generalize.

E) Tonic seizures. They are unusual in this syndrome. They may look like tonic seizures with or without a myoclonic component as seen in LGS, which are commonly sporadic. The ictal EEG shows either a decremental event or low amplitude rapid rhythms, followed by slow waves. In a recent study,\textsuperscript{30} they recorded tonic seizures in 5 patients and described an interictal EEG pattern consisting of frontal, slow, bi, or tri spikes, followed or not by slow waves, when awake, activated by sleep. They may have other epileptic events, which can be very difficult to classify.

Developmental and cognitive features. Most patients with DS have various degrees of cognitive deficits and behavioral difficulties, which are usually noted very clearly from the second year of age.\textsuperscript{31} As a rule, children start walking at a normal age but an unsteady gait develops for an unusually long period. Language also starts at a normal age, but progresses very slowly, and many patients do not reach the stage of constructing elementary sentences. Patients’ fine motor abilities are disturbed by segmental myoclonus and by poor eye-hand coordination. The most apparent problems in children with DS that hinder them from learning are attention deficit hyperactivity and difficulties in concentration. These patients are not interested in playing with educational toys and participating in the usual activities of their age group and do not listen to adults. However, they can complete puzzles and watch cartoons repetitively. Not all these traits are present in all patients, and the traits tend to be less severe in those with a recent diagnosis.\textsuperscript{24} In the first studies, the degree of impairment appeared to be correlated with the severity of epilepsy during the first 2 years of life.\textsuperscript{32}

The EEG features. Intertical EEG recordings are generally normal during the first months of the disease, despite the frequent seizures (unlike the slow spike-waves observed for LGS). As the patient gets older, various EEG features start to be evident such as multifocal, focal, or generalized epileptiform activities. In addition, the background of the EEG activity starts to become slower.\textsuperscript{4,28} From the second year of life, generalized discharges of fast spike-wave or poly spike-wave complexes appear in bursts or in isolation, sometimes with a unilateral predominance. Focal or multifocal spikes are often observed. In later life, the EEG patterns observed are variable. Multifocal spikes
or sharp-wave discharges become more common, and background tracings become slower, especially during seizure clusters. The paroxysmal EEG abnormalities are activated during slow sleep. Then the epileptic discharges later on remit and instead the EEG shows more diffuse slowing. In the few reported cases of DS during adolescents, the EEG showed frontal slowing with 2-3 Hz epileptic discharges, which are activated during sleep and become paroxysmal lasting for several seconds without clinical features associated with the EEG.30

Neuroimaging and neuropathology. Brain MRI studies in patients with Dravet syndrome and SCN1A mutations have shown abnormal findings in a small minority of patients. Some of the abnormalities noted in the brain of patients with DS are hippocampal sclerosis, cortical dysplasia, and atrophy. It is not clear if these abnormalities are specific and related to the duration, age of onset, and the frequency of the seizures in this disorder. An immunomediated etiology in DS was proposed since the few reported cases of Rasmussen syndrome and hemiclonus-hemiplegia syndrome have the SCN1A mutation. One has to consider severe epileptic encephalopathy in these cases.33

SPECT findings. Only a few SPECT or PET studies have been performed DS. A SPECT study showed areas of hypoperfusion in 8 out of 10 patients; the finding was limited to one hemisphere in 5 patients and was bilateral in the remaining 3. Areas of hypoperfusion did not clearly correlate with EEG findings.34 In terms of neuropathological findings seen in patients with DS, there is a subtle brain malformation, which is found in some cases. It is not clear if these findings correlate with SCN1A gene dysfunction. It is worth pursuing further animal and human prospective studies to find out if early diagnosis and seizure control in patients with DS may alter the clinical, imaging, or pathologic picture.35

Differential diagnosis. Febrile seizures. It is always important to distinguish the diagnosis of FS from DS at the onset of FS. The following points are in favor of DS (a) onset is always early (before one year of age); (b) seizure type is clonic and often unilateral instead of generalized and tonic; (c) seizure episodes are more prolonged and frequent, even when treated; and (d) temperature is not very high. Dravet syndrome is commonly associated with alternating focal seizures. Then, the diagnosis becomes evident with the development of mixed seizure types and the photoparoxysmal spike-wave epileptic discharges noted in these children.14 Some studies have proposed a screening test that can be used before the end of the first year.

Benign (idiopathic) myoclonic epilepsy in infancy. The first events are brief generalized myoclonic seizures, which remain the only ictal manifestations even without treatment. Usually, these children have normal development and they respond well to antiepileptic medications. Their EEG show generalized epileptic discharges associated with myoclonic jerks. They carry a good prognosis, and the reflex seizures resolve spontaneously.36

The epilepsy with myoclonic-astatic seizures (Doose syndrome). It is defined by the association of GTCS and frequent “drop attacks,” which are unusual DS, and, as a rule, it starts after the age of 2 years and has a different course. Atypical absence status with myoclonic jerks occurs, but there are no focal seizures and no focal EEG abnormalities. The outcome is variable with complete cure in >50% of the cases.37

Progressive myoclonus epilepsy. Mainly ceroid lipofuscinosis, can be evoked in the second year when neurologic and behavioral signs appear. These patients usually have visual abnormalities, abnormal evoked potential, and retinal abnormalities. A mitochondrial encephalomyopathy must be considered in the most severe cases and in the presence of metabolic changes induced by AEDs.38

Lennox-Gastaut syndrome. It is characterized by mixed seizure types such as atypical absences, drop attacks, and most commonly tonic seizures, in addition to typical EEG features. Febrile seizures are very rare in infancy. An onset of atypical FS and focal seizures can be seen in patients with early cryptogenic focal epilepsy. They may not have myoclonic or absence seizures. The EEG features are typical of focal abnormalities. The presence of hemiclonus and alternating seizures makes this diagnosis less likely.39 Interestingly, a few cases of focal epilepsy that carry similar clinical characteristics of DS may have the SCN1A mutation, such as epilepsy of infancy with migrating focal seizure.

Generalized epilepsy with febrile seizures plus family. One member may have DS. The typical clinical feature is prolonged and atypical FS, which refractory to antiepileptic drugs (AEDs) followed by psychomotor retardation. Recently, mutations in PCDH19, the gene encoding the protocadherin 19 on the X chromosome, were discovered in some of the SCN1A-negative female patients presenting with a clinical picture resembling the borderline SMEI, which was described as “Epilepsy and mental retardation limited to females (EFMR).”40 It is considered to be a variant of DS, which carry a different mutation. Therefore, in patients who are less than one year who develop atypical and frequent FS, the diagnosis of DS should be considered, which is further confirmed by the development of other mixed seizure types, photosensitivity, and developmental delay. The
borderline form of DS should also be considered when the SCN1A mutation is found.

**Treatment.** There is no single effective treatment used for these patients. This makes the treatment modalities in children with DS limited. As a preventative measure, hot baths should be avoided in young children and sunglasses or any other method to reduce photo-and pattern-sensitivity, when present, may prove useful. Vigorous treatment of febrile diseases might be of uncertain value. In general, there is a lack of controlled trials regarding the efficacy of available antiepileptic drugs (AEDs). Many AEDs have no effect and may be at the origin of adverse effects, such as carbamazepine\(^\text{41}\) and vigabatrin,\(^\text{4}\) which can favor or even induce myoclonic seizures and lamotrigine,\(^\text{42}\) particularly for young patients. For older patients, polytherapy should be avoided, and the specific action of each AED should be considered. The AEDs that have been shown to have therapeutic value against DS include valproate,\(^\text{13}\) levetiracetam,\(^\text{43}\) zonisamide,\(^\text{44}\) and topiramate,\(^\text{45}\) especially in patients who were unsatisfactorily treated with stiripentol alone.\(^\text{46}\) Stiripentol is a new AED that recently received conditional approval from the European Medicines Agency to be used throughout the European Union, in conjunction with clobazam and valproate as adjunctive therapy for refractory generalized tonic-clonic seizures in patients with DS.\(^\text{47}\) When administered as an “add-on,” stiripentol demonstrates a positive effect on reducing the frequency of seizures.\(^\text{47}\) A systematic review and meta-analysis of individual data demonstrated a positive effect of stiripentol in patients with DS using 23 uncontrolled studies and 2 randomized controlled trials. The efficacy of stiripentol in patients with DS is ~70% compared with placebo.\(^\text{48}\) This seems to have promising results. Other treatment modalities used in patients with DS include vagus nerve stimulation (VNS), ketogenic diet (KGD), bromide, immunoglobulins, and steroids.\(^\text{49,50}\)

Most of the preceding reports refer to anecdotal cases or to open studies.

**Comorbid conditions. Autism spectrum characteristics and communication impairments.** Many surveys in the literature demonstrated the developmental delay, psychomotor regression, behavioral difficulties, language and communication problems, autistic features, and sensory integration abnormalities in affected patients with DS.\(^\text{51}\)

**Cardiovascular.** Various cardiac abnormalities have been described in patients with DS and their families, which includes prolonged Q-T interval, tachycardia or bradycardia, tricuspid atresia, bicuspid aortic valve, atrial septal defect, and pulmonary stenosis. These associated abnormalities may resolve spontaneously in the first year of life.\(^\text{51}\)

**Dental health.** These patients may have malocclusion (13%), delayed teething (20%), bruxism (20%), and a few children with DS may have malformed teeth and oral infections.\(^\text{51}\)

**Dysautonomia.** Autonomic dysfunction is seen commonly in children and families with DS such as papillary dilatation, episodes of flushing, stomach emptying difficulties, regulation of body temperature, and sweating.\(^\text{52}\)

**Coordination, growth, and nutrition.** It is very common for patients with DS to have failure to thrive (22%), feeding difficulties, and an orthopedic disorder such as pes planus and/or pes valgus foot deformities. They also may have hypotonia (56%), hypertonia (14%), joint laxity (21%), ataxia, and constipation (29%).\(^\text{52}\)

**Infections and immune dysregulation.** Infections of the respiratory tract are frequently reported; gastritis and urinary tract infections are also of concern. Thirteen percent of patients with DS are found to have immune problems.\(^\text{52}\)

**Sleep.** Sleep disorders are seen commonly in these patients, which include insomnia (20%), premature awakening (28%), nocturnal seizures (50%), and sleep apnea (52%).

**Mortality and sudden unexpected death in epilepsy.** The mortality rate was reported as 3.7%.\(^\text{52}\) The mean age of death was 4.6 years (range 10 months to 17 years); the most frequent age of death was 2 years. The causes of death are SUDEP (61%), and SE (32%). Few died from ketoacidosis and seizure-related accidents. There was no significant relationship between death, gender, or country of residence. In 2009, the death rate by year joined ranged from 2.3-4.9%.\(^\text{52}\)

**References**

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