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From genotype to phenotype in Dravet disease

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ABSTRACT

Dravet syndrome combines clonic generalized, focal or unilateral seizures, beginning within the first year of life, often triggered by hyperthermia whatever its cause, including pertussis vaccination. Long-lasting febrile seizures are frequent in infancy and repeat status epilepticus (SE) has negative prognostic value. Massive myoclonus, rare absences, complex partial seizures and generalized spikes may appear several years later. Myoclonic status may occur in childhood, but acute encephalopathy with febrile SE followed by ischemic lesions and psychomotor impairment, the most severe condition, occurs mainly within the first five years of life. Generalized tonic–clonic and tonic seizures in sleep predominate in adulthood. Non epileptic manifestations appear with age, including intellectual disability, ataxia and crouching gait. Incidence of SUDEP is high, whatever the age. *SCN1A* haploinsufficiency producing $Na_V1.1$ dysfunction mainly affects GABAergic neurons. In cortical interneurons it explains epilepsy, in cerebellum the ataxia, in basal ganglia and motor neurons the crouching gait, in hypothalamus the thermodysregulation and sleep troubles, and dysfunction in all these structures contributes to psychomotor delay. Valproate, stiripentol, topiramate and bromide are the basis of antiepileptic treatment, whereas inhibitors of sodium channel worsen the condition. Benzodiazepines seem to facilitate acute encephalopathy when given chronically, and they should be restricted to SE. Ketogenic diet is useful in both chronic and acute conditions. Only targeting *SCN1A* haploinsufficiency and $Na_V1.1$ dysfunction could improve non epileptic manifestations of this condition that deserves being considered as a disease, not only as an epilepsy syndrome.

1. Introduction

Among rare and severe epilepsies, Dravet syndrome (DS) occupies a particular place that is well expressed by the names it was given along its short history. Initially "Severe myoclonic epilepsy of infancy" (SMEI) was distinguished from Lennox–Gastaut syndrome (LGS) which was then considered as the most common severe epilepsy of childhood, and with which it shared pharmacoresistance, drop attacks, episodes of status epilepticus (SE) and intellectual disability [1]. Charlotte Dravet noticed that some children wrongly labeled as LGS exhibited massive myoclonus with photosensitivity and had had febrile seizures (FS) from the first year of life, thus pointing to a previously overlooked condition. Later, when it appeared that myoclonus was missing in over half the cases, the condition received the eponym of DS. Since then, its molecular basis has been identified [2]. It is now increasingly clear that epilepsy is the tip of the iceberg and that cognitive delay is another expression of the mutation, not merely the consequence of seizures. DS also produces age-dependent movement disorders, to which central and peripheral nervous systems contribute. Furthermore, there is not only neurological but also cardiac impact. Should it therefore still be considered as an epilepsy syndrome or more likely as a disease?

2. Clinical features

2.1. Epilepsy

DS affects 1/15.700 to 1/40.000 [3], 1.4% of children with epilepsy. Charlotte Dravet identified 3 stages in the course of DS [1]. The first, "*febrile stage*" is specific enough to permit high

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diagnostic probability within the first year of life. First seizure occurs before 12 months of age in over 90% of cases, usually between 4 and 8 months, in a child previously considered as developing normally and without neurological history. It is clonic, generalized, focal or unilateral, prolonged in one third of the cases, triggered by mild fever or hot bath. This complicated FS often follows pertussis vaccination. 2.5% of patients with seizures following vaccination develop DS. Many patients previously labeled "post-vaccination encephalopathy" carry *SCN1A* mutation, and disease course is similar to that of patients with DS whose first seizures was not triggered by vaccination [4]. Prior to repeat seizures, mild hyperthermia, 37.5–38.5 °C, is often not noticed by the surrounding and muscle activity including that due to the seizure itself may have contributed to rising temperature. 80% of patients have hemi-clonic and/or focal seizures, lasting over 15 min. Rectal/oral benzodiazepine (BZ) often fails to stop the seizure that requires admission to hospital. Seizure frequency is moderate at onset, once a month or even less until the end of the first year of life. Seizures may repeatedly affect the same body area for several months, misleadingly pointing to possible focal epilepsy but interictal electroencephalogram (EEG) shows no spikes for several years and theta activity becomes prominent in the second year of life [5]. In very rare instances, massive myoclonic jerks are the first seizure type, before clonic seizures occur.

Between 1 and 5 years of age, in the "*worsening stage*", motor seizures become more frequent but shorter, although their severity is still linked to mild hyperthermia. They affect randomly various parts of the body, a sequence indicating that the whole motor strip is involved. A triggering factor can often be identified: mostly hyperthermia, but also physical exercise, emotion, whereas light is less frequently a trigger than used to be when the condition was first described. Some patients nevertheless exhibit self-stimulation, watching the sun and closing the eyes. Fever remains a major cause of anxiety for parents who each time fear a new seizure.

Several months after onset, additional seizure types appear (Fig. 1), in less than half the cases, namely myoclonus and absences [6]. Myoclonic jerks can be massive or erratic. Absences and complex partial seizures without any motor component are rare and their recognition requires ictal EEG. Generalized 2–3 Hz spike-waves can be seen on EEG after 3–5 years. Photosensitivity occurs in a small proportion of cases, namely in patients with massive myoclonus.

By the end of the first decade, the "*stabilization stage*" begins in which seizures are less frequent, are brief, occur in sleep, and are tonic in a small proportion of cases. It is only at the end of the first decade that in a small proportion of cases EEG shows bursts of high frequency generalized spikes distinct from slow spike waves of the LGS [7]. Cognitive troubles are now in the front scene. In milder forms seizures become rare, down to 1/year, but they rarely disappear completely. These cases exhibit better cognition with valuable speech.

Although conventional MRI identifies no abnormality in neocortex, basal ganglia and white matter, morphometry in the second decade showed global volume reduction of gray and white matters in brainstem, cerebellum, corpus callosum, corticospinal tracts and association fibers. Hippocampal atrophy following long lasting unilateral FS is a rare finding.

Various types of *Status Epilepticus* may occur: (1) in infancy, prolonged clonic FS, often unilateral, commonly last over 30 min; (2) between 4 and 8 years of age, obtundation (non-convulsive) status with confusion combined with erratic myoclonus of the extremities and around the mouth lasting several hours is associated with pseudo-rhythmic slow wave activity encroached with irregular spikes. (3) In addition to these transient events, severe febrile SE lasting several hours or days, usually quoted as "acute encephalopathy" remains an etiological challenge. It occurs with non-specific infection, usually within the first five years of age, several months or years after onset of epilepsy in patients chronically treated with BZ combined with valproate (VPA) [8]. To manage the SE, all patients received high doses of BZ and about half got barbiturates. Cortical, basal ganglia and white matter lesions, consistent with acute ischemia, sustain severe psychomotor sequelae with spastic tetraparesis and cognitive impairment.

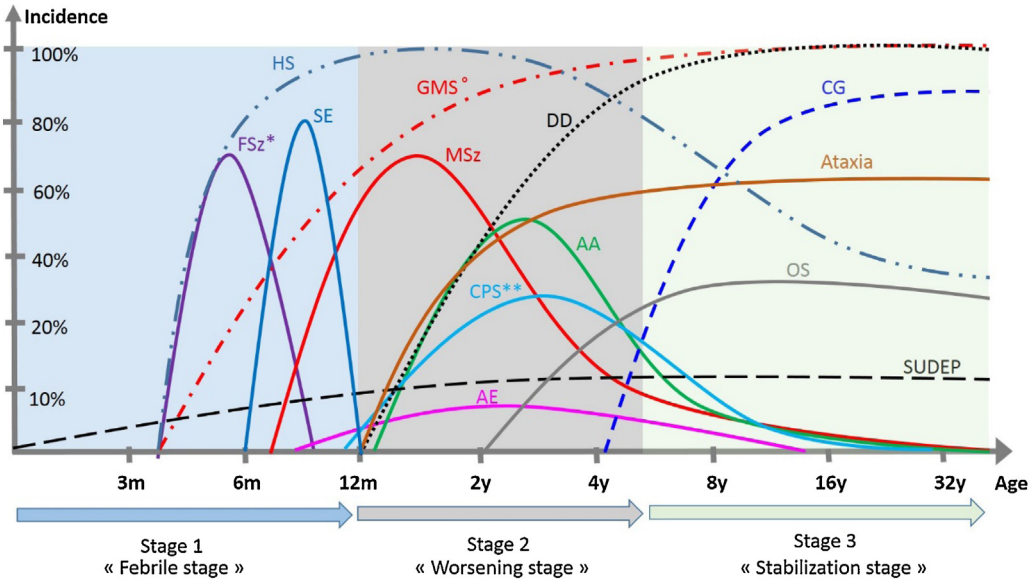

Fig. 1. Schematic representation of clinical manifestations of Dravet syndrome and their relative incidence according to age.
FSz—complex febrile seizures [6]; HS—hyperthermia sensitivity [9,16]; SE—convulsive status epilepticus [6]; GMS—generalized motor seizures [1]; MSz—myoclonic seizures [6]; AA—atypical absences [6,9]; CPS—complex partial seizures [1,6]; OS—obtundation status [1]; AE—acute encephalopathy [8]; DD—developmental delay [6]; CG—crouching gait [12]; Ataxia [1]; SUDEP—Sudden unexpected death in epilepsy [14]; *Moderate fever for 60% [1]; mostly clonic generalized and unilateral motor seizures; **Difficult distinction between atypical absences and complex partial seizures without ictal EEG recording, so their precise incidence is unknown; °Including generalized tonic–clonic and unilateral seizures [1]. However, unilateral seizures are less frequent after the age of 7 years, whereas sleep seizures increase after 6–7 years, and become predominant after age of 9–10 years [1].

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