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The core Dravet syndrome phenotype

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Summary

Dravet syndrome was described in 1978 by Dravet (1978) under the name of severe myoclonic epilepsy in infancy (SMEI). The characteristics of the syndrome were confirmed and further delineated by other authors over the years. According to the semiologic features, two forms have been individualized: (1) the typical, core, SMEI; and (2) the borderline form, SMEIB, in which the myoclonic component is absent or subtle. Clinical manifestations at the onset, at the steady state, and during the course of the disease are analyzed in detail for the typical Dravet syndrome, and the differential diagnosis is discussed. Onset in the first year of life by febrile or afebrile clonic and tonic–clonic, generalized, and unilateral seizures, often prolonged, in an apparently normal infant is the first symptom, suggesting the diagnosis. Later on, multiple seizure types, mainly myoclonic, atypical absences, and focal seizures appear, as well as a slowing of developmental and cognitive skills, and the appearance of behavioral disorders. Mutation screening for the *SCN1A* gene confirms the diagnosis in 70–80% of patients. All seizure types are pharmacoresistent, but a trend toward less severe epilepsy and cognitive impairment is usually observed after the age of 5 years.

KEY WORDS: Severe myoclonic epilepsy in infancy, SMEI, SMEIB, Seizures, Diagnosis, Evolution.

Historical Introduction and Definition

The Dravet syndrome is a rare form of epilepsy, and is accompanied by impaired psychomotor and neurologic development, occurring in the first year of life in apparently normal infants. It was initially described in 1978 (Dravet, 1978), as severe myoclonic epilepsy of infancy (SMEI) in order to distinguish it from the Lennox-Gastaut syndrome (LGS). In the following years, several authors reported similar cases in Europe and in Japan (Dalla Bernardina et al., 1982; Ogino et al., 1986). It became progressively obvious that these cases represented a subset of patients with the same epilepsy syndrome. From the end of the 1980s and onward, some degree of variability between patients was noted, particularly for the myoclonic syndrome, which could be absent (Ogino et al., 1989; Dravet et al., 1992; Kanazawa, 1992; Yakoub et al., 1992). These patients may have different electroencephalographic (EEG) features but they share the same course and outcome as patients having myoclonic seizures and can be included in the same syndrome as borderline forms (SMEIB). It also appeared that the epilepsy was not limited to infancy and childhood but persisted through adulthood. For these reasons, the use of the eponym ''Dravet syndrome'' was proposed (Commission on Classification and Terminology of the International League Against Epilepsy, 1989).

Since 2001, the discovery of *SCN1A* mutations in most affected patients changed the syndrome into a disease, a channelopathy (Claes et al., 2001), and other questions arose such as: Is there a single disease with different forms related to different mutations? Is this disease part of a large spectrum including other myoclonic and nonmyoclonic epilepsies? What are the respective roles of epilepsy and mutations in cognitive and motor development? In the scheme proposed by the International League Against Epilepsy (ILAE) (Engel, 2001), the Dravet syndrome is considered as an ''epileptic encephalopathy,'' defined as a condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function. However, it is not proven that the cognitive

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decline observed in the first stages of the disease is the consequence of the epilepsy.

According to the ILAE classification (1989), the typical Dravet syndrome, is defined by ''febrile and afebrile generalized and unilateral, clonic or tonic–clonic, seizures, that occur in the first year of life in an otherwise normal infant and are later associated with myoclonus, atypical absences, and partial seizures. All seizure types are resistant to antiepileptic drugs (AEDs). Developmental delay becomes apparent within the second year of life and is followed by definite cognitive impairment and personality disorders.''

General Description

Epidemiology

Dravet syndrome is rare but its actual frequency is not well known. An incidence of probably <1 per 40,000 live births was reported in 1990 in the U.S.A. (Hurst, 1990). Slightly different figures (1/20,000 or 30,000) were reported by Yakoub et al. in France (1992). The rate of Dravet syndrome in epilepsy children aged <15 years is also low: 1.4% in the most recent study in Spain (Durà-Travé et al., 2007). Even if the recognition of the syndrome has increased in the last decade, Dravet syndrome remains rare.

Family history

A large proportion of patients have a family history of epilepsy or febrile seizures (FS), but there is high variability reported among the authors—from approximately 25% to approximately 71%. In many studies the relationship with genetic abnormalities was not investigated. In other studies with genetic analysis, the results are equally variable: 27% in patients bearing *SCN1A* mutations (Mancardi et al., 2006), 51.2% in mutation-positive patients, and 62.5% in patients with no demonstrable mutation (Marini et al., 2007).

Personal antecedents and associated pathology

The infants usually do not have significant personal pathologic history. However, more or less relevant antecedents during pregnancy and delivery were reported in 22–40% of the patients (Dravet et al., 1992; Ragona et al., 2010). An associated disease was observed in rare patients: Rud syndrome in one, type I neurofibromatosis in one (Dravet et al., 2005), congenital cardiac defect in two, growth hormone deficit in two, and hemophilia in one (personal data). The early development is apparently normal, even in the patients with pathologic antecedents.

Semiology at Onset

Dravet syndrome begins during the first year of life in a normal baby who presents with one convulsive seizure, related or not to fever or vaccination. All authors indicate an age at onset between 5 and 8 months. Onset after 1 year has been exceptionally reported (Kearney et al., 2006). The first seizure is typically clonic, generalized, or unilateral, triggered by fever and longer than a simple febrile seizure. Several Japanese authors (Ogino et al., 1989; Fujiwara et al., 1990) underscored the triggering effect of a Japanese style hot water immersion, which produces a body temperature elevation.

However, some variability in the mode of onset has been reported. Convulsive seizures can occur without fever in from 28% (Ohki et al., 1997) to 35% (Dravet et al., 2005) and 61% (Ragona et al., 2010) of the patients. In our 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 febrile seizures. These seizures, with or without fever, tend to be prolonged, lasting longer than 20 minutes, in 25% (Dravet et al., 2005) to 49% (Ragona et al., 2010) of the patients, and to evolve into status epilepticus. 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. They appear without any fever and remain isolated, or occur in the hours preceding the first convulsive seizure, repetitively, together with hyperthermia.

At this stage of the disease EEG is usually normal both while awake and during sleep. EEG recordings may show diffuse or unilateral slowing of the background if they are recorded after a prolonged seizure. In some patients they can show generalized spike waves (SWs), either spontaneous or elicited by the intermittent photic stimulation (IPS) (Dalla Bernardina et al., 1982; Dravet et al., 1992). Rhythmic theta activities at 4–5 Hz can be present in the centroparietal areas and over the vertex (Dalla Bernardina et al., 1982).

The first seizure is often considered a FS or an accidental seizure; few investigations are performed and no treatment is given. However, shortly thereafter (2 weeks to 2 months), other febrile seizures occur and afebrile seizures also appear. Between age 1 and 4 years, other seizure types appear, simultaneously with slowing of the development, and the picture becomes characteristic of a steady state.

Steady State

Seizures

Patients with Dravet syndrome have multiple seizure types: (1) convulsive seizures consisting of generalized clonic seizures (GCS), generalized tonic–clonic seizures (GTCS), or alternating unilateral clonic seizures; (2) myoclonic seizures; (3) atypical absences and obtundation

status; (4) focal seizures, with or without secondary generalization; or (5) rarely, tonic seizures.

1 Convulsive seizures, apparently generalized or unilateral, are present throughout the evolution in all patients. Video-polygraphic EEG recordings show that most seizures are not truly generalized but rather secondarily generalized after a brief, often unnoticed, focal onset, or they are ''unstable'' from one hemisphere to the contralateral. Unilateral seizures are the most characteristic. In the youngest patients, they correspond to hemiclonic seizures (Gastaut et al., 1974) and often evolve to status. In older patients they are shorter, with association of contralateral tonus changes. In all cases there are postictal asymmetric EEG signs and, often, postictal transitory hemiparesis. These seizures can be on either side in the same patient, this alternating pattern being a clue for the diagnosis of DS. These seizures can be prolonged or repeated, realizing status epilepticus, requiring intravenous drug administration and, often, respiratory assistance.

2 Myoclonic seizures (myoclonic jerks corresponding to a paroxysmal discharge on the EEG) appear between the ages of 1 and 5 years (mean 1 year 5 months). They can be massive, involving all muscles, particularly the axial ones. Their intensity is variable. When they are violent they lead to hurling of objects held by the child, and falling. But they are sometimes barely discernible, involving only the axial muscles (head and trunk), with an atonic component, giving a small movement forward or backward, more or less saccadic, described as a ''head nodding.'' They are either isolated or grouped in brief bursts (1–3 s) and are very frequent, occurring several times a day, sometimes incessantly. Conversely, in some children they are observed only on awakening or in the minutes or hours preceding a convulsive seizure. They persist during drowsiness and disappear during slow sleep. Photic stimulation, variation in light intensity, closure of the eyes, and fixation on patterns are precipitating factors. There seem to be no accompanying change in consciousness, except when myoclonic seizures occur at close intervals or in long bursts (up to10 s). In our series, the occurrence of myoclonic status is rare. Other authors describe these statuses in their patients, sometimes lasting more than 1 day (Dalla Bernardina et al., 1987; Yakoub et al., 1992).

3 Atypical absence seizures can appear at different ages, between 4 months and 6 years (Ohki et al., 1997), together with myoclonic attacks, or later on, up to the age of 12 years. Their duration varies from 3–10 s. They are characterized by impairment of consciousness, either isolated or accompanied by a more or less obvious myoclonic component such as rapid eyelid myoclonia, realizing an ''eye fluttering,'' head nodding, and forehead myoclonic jerks. When the myoclonic component is pronounced, it is difficult to differentiate these atypical absences from myoclonic attacks. In fact, both are probably the expression of the same epileptic process with different intensity and duration. The obtundation status represents a relatively characteristic symptom, reported in several series (40% for Dalla Bernardina et al., 1987; 30% for Dravet et al., 2005). It consists of impairment of consciousness, variable in intensity, with fragmentary, segmental, and erratic myoclonus, of low amplitude, involving the limbs and the face, sometimes associated with a slight increase of the muscle tone. According to the degree of consciousness, patients can or cannot react to stimuli and perform simple activities (manipulate toys, eat), interrupted by short episodes of complete loss of contact and staring. Strong sensory stimulations can interrupt the status but never definitively. Some episodes can last for several hours, even days, maintained by environmental light stimuli, eye closure, and pattern fixation (dotted lines of the walls, TV screen, and so on). Convulsive seizures can initiate, occur during, or terminate this status. Two authors reported nonconvulsive status corresponding to focal occipitotemporal region status (Wakai et al., 1996; Oguni et al., 2001). Surprisingly, obtundation statuses were not reported in the two recent studies (Caraballo & Fejerman, 2006; Ragona et al., 2010).

4 Focal seizures consist of motor seizures or seizures with more complex semiology, including prominent autonomic symptoms. They occur in 43–78.6% of patients in the largest series (Oguni et al., 2001; Dravet et al., 2005; Ragona et al., 2010), from 4 months to 4 years (Ohki et al., 1997). In our series, focal motor seizures were manifested as either versive seizures or clonic jerks limited to a limb or a hemiface, or a combination of the two. Other focal seizures were characterized by loss of consciousness, autonomic phenomena (pallor, cyanosis, rubefaction, respiratory changes, drooling, sweating), oral automatisms, hypotonia, and rarely stiffness, sometimes with eyelid or distal myoclonus. When the symptomatology is mild it is difficult to distinguish the seizures from atypical absences without concomitant EEG. The seizures occur in patients who have one or several foci, in the posterior and frontal brain areas. The two focal seizure types can secondarily generalize. In the literature, the reported focal seizures are usually of the second type, with the same characteristics we described (Ohki et al., 1997).

5 Tonic seizures are unusual in this syndrome. They resemble the axial tonic seizures of the LGS, sometimes with a myoclonic component, but they are usually sporadic, and only in three cases in our series were they frequently repeated during the same recording, as in the LGS. Ictal EEG shows either a decremental event or low amplitude rapid rhythms, followed by slow waves,

or a rapid recruitant rhythm, sometimes interrupted by a decremental event. Only in two cases interictal sleep EEG was analogous to that in the LGS (rapid rhythms and multiple SWs). In a recent study, Nabbout et al. (2008) recorded tonic seizures in five 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.

Other ictal events are sometimes described by the parents, which could be epileptic in nature but are difficult to classify.

Provocating factors

One must underscore the great value of the triggering factors. The provocating effect of slight temperature variations, without true fever, and of infections is characteristic and present all along the life span. Febrile epileptic status can occur up to adulthood. Photo and pattern sensitivity are also frequent, including environmental light, and lead to autostimulation, sometimes simply by eye closure. Photo and pattern sensitivity are variable during the course of the disease. Many other stimuli may trigger seizures: hot baths, physical exercise, noisy environments, emotions, and other individual stimuli. This high convulsive susceptibility is a factor of pharmacoresistance.

Developmental and cognitive features

Cognitive deficits and behavioral disturbances are a common trait. They are relatively homogeneous in quality but of different degrees (Cassé-Perrot et al., 2001; Wolff et al., 2006). Developmental delay becomes progressively evident from the second year on. 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 do not develop well. They are disturbed by segmental myoclonus and by poor eye–hand coordination. Even patients with milder cognitive impairment cannot draw a design and write only by printing letters. Lack of attention is one of the major factors responsible for the learning disabilities, as well as for hyperactivity and recalcitrant behavior. Affected children are restless, do not listen to adults, and are not interested in playing with educational toys and participating in the usual activities of their age group. Conversely they are able to complete puzzles and to 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 (Buoni et al., 2006; Ragona et al., 2010). In the first studies, the degree of impairment appeared to be correlated with the severity of epilepsy during the first 2 years of life. This correlation was not confirmed by the ongoing study, the results of which are presented in this issue (Ragona et al., 2011; Ragona, 2011).

Neurologic signs

At the very onset, the infants are apparently normal. The neurologic signs appear progressively, simultaneously with the developmental delay, but are not observed in all patients. The signs consist of hypotonia, ataxia (60%), pyramidal signs (20%), uncoordinated movements, and interictal myoclonus. Their course is variable. The facial muscle hypotonia can make chewing and swallowing difficult. Ataxia tends to attenuate with age but it may again appear after status epilepticus or worsening of seizures and increase along the years. The association of hypotonia and ataxia leads to a peculiar way of walking and running, as if the children had ''spaghetti legs,'' as written by a mother. Kyphoscoliosis and club feet are frequent, worsening with age, and are responsible for walking difficulties.

Course of the disease

Despite recent advances, treatment remains a challenge and seizure control is often partial and transitory. Few AEDs are actually useful, such as valproate, benzodiazepines, stiripentol, topiramate, bromides, and maybe levetiracetam (see Chiron and Dulac, 2011). The ketogenic diet is also an option (Caraballo, in this issue). Three principles are essential: to apply prophylaxis against infections and temperature variations; to avoid AEDs that can worsen the seizures, lamotrigine and carbamazepine; and to stop the convulsive seizures before they evolve into status. However, three stages can be distinguished: (1) the febrile or diagnostic stage in the first year; (2) the worsening (preferred to ''catastrophic'') stage between 1 and 5 years: period with frequent seizures and statuses, behavioral deterioration, and neurologic signs; and (3) the stabilization stage after 5 years: convulsive seizures decrease and occur mainly in sleep, myoclonic and absence seizures can disappear, focal seizures persist or decrease; mental development and behavior tend to improve but cognitive impairment persists, although of variable degree. But there are exceptions, and worsening of epilepsy and behavior is not excluded after the age of five. In 1992 (Dravet et al., 1992), we found a high rate of early mortality : 15%, due to accidents, drowning, severe status, infections, and sudden unexplained death (SUDEP), but this rate has probably decreased in the last years (see Sakauchi et al., 2011).

Differential Diagnosis

Because the first clonic seizures in Dravet syndrome are often associated with fever, distinction from febrile seizures is important. In Dravet syndrome (1) onset is always early (before 1 year of age); (2) seizure type is clonic and often unilateral instead of generalized and tonic; (3) seizure episodes are more prolonged and frequent, even when treated; and (4) temperature is not very high. The alternat-

ing character of unilateral seizures is in favor of Dravet syndrome. The diagnosis can be made when other seizure types (myoclonic seizures— except in the borderline forms—atypical absences, focal seizures, obtundation statuses) or photic-induced SWs appear (Dravet et al., 2005). Hattori et al. (2008) have proposed a screening test that can be used before the end of the first year.

In the benign (idiopathic) myoclonic epilepsy in infancy (Dravet & Vigevano, 2008), the first events are brief generalized myoclonic seizures, which remain the only ictal manifestations even without treatment. Rare simple FS are associated in some patients. EEG studies always show generalized SWs concomitant with the jerks. Seizures are pharmacoresponsive, development is normal or slightly retarded, and prognosis is favorable. The reflex form with contact-induced myoclonic seizures can recover spontaneously.

The epilepsy with myoclonic–astatic seizures (Doose syndrome) is defined by the association of GTCS and frequent ''drop attacks,'' which are unusual in Dravet syndrome, 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. Outcome is variable with complete cure in >50% of the cases (Guerrini et al., 2005).

Progressive myoclonus epilepsy, mainly ceroid-lipofuscinosis, can be evoked in the second year when neurologic and behavioral signs appear. It can be ruled out by absence of visual loss, fundus abnormalities, posterior-evoked potentials elicited by the IPS low frequencies and negative results of biologic investigations. A mitochondrial encephalomyopathy must be considered in the most severe cases and in presence of metabolic changes induced by AEDs (Castro-Gago et al., 1997).

The Lennox-Gastaut syndrome is virtually excluded by a history of febrile clonic seizures in the first year of life. Its characteristics are different: frequent lesional etiology, later onset, drop attacks, atypical absences, axial tonic seizures, and specific electroencephalographic abnormalities, with diffuse slow spike-waves and rapid, high-voltage rhythms during sleep.

Early cryptogenic focal epilepsy may have the same onset with complicated FS rapidly associated with focal seizures. These patients do not present atypical absences or myoclonic jerks. The focal EEG abnormalities tend to have a constant topography. This diagnosis is unlikely when hemiclonic seizures affect either hemisphere alternatively and when partial motor seizures affect different parts of the body (Sarisjulis et al., 2000). However, rarely patients have been reported with focal epilepsy sharing clinical features with Dravet syndrome and also carrying an *SCN1A* mutation (Harkin et al., 2007; Okumura et al., 2007). These cases raise the problem of the limits of the Dravet syndrome.

In the context of a generalized epilepsy with febrile seizures plus family (Scheffer & Berkovic, 1997), one member may have Dravet syndrome. This diagnosis must be affirmed when the patient presents with early, severe, pharmacoresistant FS associated with other seizure types and developmental 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)'' (Scheffer et al., 2008). We believe it is a Dravet syndrome variant of which the differences seem to be the result of a different mutation (see Marini et al., in this issue).

Therefore, in an infant younger than 1 year, the occurrence of repeated and prolonged FS must suggest the diagnosis of Dravet syndrome, which will be affirmed after the appearance of other elements: other seizure types such as myoclonic, atypical absences, focal seizures, delay in development, photosensitivity. The presence of an *SCN1A* mutation provides a strong argument, particularly in the borderline forms.

Conclusion

In 1978 we described an epileptic syndrome of unknown etiology, different from other epileptic encephalopathies. In 2010 we know this syndrome is caused by a channelopathy, which causes a complex epilepsy and more or less severe cognitive impairment, the causative factors of which are still unclear. If the diagnosis is relatively easy in many infants who present with all the typical semiology, it becomes difficult in other situations when the clinical expression is incomplete, when epilepsy is not very severe, and/or when development is almost normal. The presence of an *SCN1A* mutation is an important diagnostic element, but the relationships between phenotype and genotype are not yet elucidated and the diagnosis should remain clinical. Not all patients carrying an *SCN1A* mutation have Dravet syndrome.

Although patients' histories are similar, their individual characteristics are variable: seizure types, triggering factors, developmental and cognitive skills, response to drugs, long-term outcome, comorbidities (behavioral, orthopedic, and so on). Every child is a person, with his own genetic and acquired characteristics, and must be considered as unique and treated according to his own personality.

Disclosures

Dr. Charlotte Dravet is a member of the scientific advisory board of the Biocodex and is appointed by Biocodex as an occasional expert.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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