Dravet syndrome (DS), otherwise known as severe myoclonic epilepsy of infancy (SMEI), is a severe form of epilepsy in which the clinical diagnosis can be genetically confirmed in around 85% of patients. Since first being described, DS has been increasingly recognized worldwide; yet it remains a rare disorder with an incidence of probably less than 1 per 40,000. Its prevalence in children with seizure onset in the first year of life varies between 3 and 8%. The definition of DS actually designates a spectrum of conditions with variable severity, all appearing in children whose development before seizure onset was deemed normal. Of course, there are methodological limitations in organizing prospective studies that would unequivocally demonstrate the complete integrity of early development. Within this spectrum, in addition to the severe, classical phenotype, ‘borderline SMEI’ (SMEB) forms are also included, in which patients share most but not all the characteristic clinical features.

According to many authors, DS fully illustrates the concept of epileptic encephalopathy, a condition in which seizures and epileptiform abnormalities or both contribute to the progressive disturbance in cerebral function. As such, epileptic encephalopathies represent more a concept and an operational category, rather than a syndrome spectrum. For most conditions included in this category, there are no established endpoints for treatment, and drug choices are empirically established. In many individuals, the underlying cause, which often remains unrecognized, probably plays a greater role than is acknowledged in determining cognitive outcome. DS is no exception, as it is still unclear to what extent the underlying ion channel dysfunction and the outcome. DS is no exception, as it is still unclear to what extent the underlying ion channel dysfunction and the outcome. DS is no exception, as it is still unclear to what extent the underlying ion channel dysfunction and the outcome. DS is no exception, as it is still unclear to what extent the underlying ion channel dysfunction and the outcome.

The initial manifestations are seen before 12 months of age, with repeated generalized or unilateral clonic (hemiconic with alternating side) seizures, typically triggered by fever. Seizures are often prolonged, tend to recur in clusters in the same day and may evolve into status epilepticus. Factors that raise body temperature, such as vaccinations or hot water immersion, can precipitate seizures. Between the ages of 1 and 4 years, additional seizure types appear including myoclonic, absences, focal and, rarely, tonic seizures. About 40% of patients experience non-convulsive status epilepticus characterized by unresponsiveness of variable intensity, with erratic myoclonic jerks. Around the second year of life, developmental slowing or stagnation becomes obvious in most patients. Behavioral disturbances with hyperactivity and autistic traits are common. The frequency of convulsive seizures seems to correlate with the severity of developmental delay. Early onset of absence and myoclonic seizures might carry a higher risk of severe cognitive impairment. Seizures persist into adulthood but are less frequent, rarely prolonged and are usually confined to sleep. During the course, cognitive and motor functions may slightly improve but remain at low levels. The mortality rate is around 16%, mainly as a result of sudden death or seizure-related accidents.

A family history of epilepsy is often found. Affected relatives usually exhibit epilepsy phenotypes that are consistent with the generalized epilepsy with febrile seizure plus (GEFS+) spectrum. An overwhelmingly high number of SCN1A mutations have been associated with DS, including the borderline forms. The frequency of detectable mutations is around 70–80%; truncating mutations account for nearly 50% of the abnormalities, with the remaining comprised of splice site and missense mutations. Intragenic deletions and whole gene deletions including only SCN1A and contiguous genes account for 2–3% of all cases and for about 12.5% of those exhibiting no point mutations. Duplications and amplifications involving SCN1A are additional rare molecular mechanisms. Most mutations are de novo, but familial SCN1A mutations also occur. Somatic mosaic mutations have been reported in some patients and should be considered when estimating the recurrence.

Some general genotype-phenotype correlations have been suggested. Truncating, nonsense, and frame shift mutations and partial or whole gene deletions are correlated with a conventional Dravet syndrome phenotype and appear to be
significantly correlated with earlier age of seizure onset.\textsuperscript{20} The severity of the phenotype is also correlated with SCN1A missense mutations falling into the pore forming region of the sodium channel, while missense changes associated with the GEFS+ spectrum are nearly always localized outside the pore forming region.\textsuperscript{21} Mutations are randomly distributed across the SCN1A protein, both in DS and GEFS+ epilepsies. Screening for the PCDH19 gene should be done in patients with DS in whom no SCN1A abnormalities can be found,\textsuperscript{22–24} as some patients with this gene mutation exhibit epileptic encephalopathy that can mimic DS.

A major question is whether seizure induced brain damage occurs in DS. There have been reports of families in which, amongst the individuals carrying SCN1A gene mutations, those that experienced a limited number of seizures had normal cognition, while those with intractable epilepsy were cognitively impaired.\textsuperscript{19,25} Ataxic gait, or motor awkwardness and hyperactivity, and a jerky movement pattern have also been reported in many children who have had severe seizures. Since genetic abnormality does not appear sufficient to cause the impairment per se, it is plausible that other factors, possibly seizure-related, might contribute to cognitive impairment. Heterozygous Scn1a+/- mice exhibit spontaneous seizures that are highly dependant on the genetic background.\textsuperscript{26} In this animal model, the sodium current density is substantially reduced in inhibitory GABAergic interneurons but not in the excitatory pyramidal neurons. Reduced sodium currents in inhibitory interneurons decrease their ability for sustained action potential firing, which would reduce their GABAergic output and enhance the excitability of their downstream synaptic targets, thus leading to epilepsy. The observation of variable penetrance of the epileptic phenotype in different genetic backgrounds correlates with the variable penetrance observed in humans and supports the notion that modifier genes are necessary for DS to appear. However, such modifier genes might also influence cognitive functioning.

Striano et al.\textsuperscript{27} and Catarino et al.\textsuperscript{28} found that MRI imaging is usually normal or shows non-specific findings, including cerebral and cerebellar atrophy, or cerebellar atrophy alone. In an extensive post-mortem neuropathological study of three adult cases, no histological signature of the condition was identified, and there was no evidence of cerebral neurodegeneration.\textsuperscript{28} In particular, no significant alteration was found in the distribution and morphology of inhibitory interneuronal subsets in the cortex, cerebellum, brainstem or hippocampus of adults with DS, even after quantitative analysis. Routine histological staining detected cerebellar atrophy with Purkinje cell loss and gliosis in all adult post-mortem cases. However, as the authors pointed out, cerebellar atrophy was a frequent finding but did not differ, either in pattern or distribution, from that previously described in patients with chronic epilepsy without DS.\textsuperscript{28} A striking feature was the conspicuous preservation of neurons and interneurons, despite decades of poorly controlled seizures.

Sakakibara et al.\textsuperscript{20} reported a 2-year-old girl who had experienced repeated episodes of febrile status epilepticus during infancy, and myoclonus, which was consistent with a clinical diagnosis of DS; she also had a nonsense mutation in SCN1A, developing persistent right hemiplegic seizures and left unilateral cortical laminar necrosis, followed by progressive cerebral atrophy at age 15 months. The clinical and neuroradiological picture was consistent with hemiconvulsion-hemiplegia (HH) syndrome. This observation confirms the potential, though exceedingly rare, risk in children with DS for developing structural changes that can subsequently be the substrate for epileptic encephalopathy. Ohamori et al.\textsuperscript{31} reported a patient with typical Rasmussen encephalitis, in whom an SCN1A-R1575C mutation (carried by the unaffected father) was fortuitously identified. The R1575C mutant channels, transiently expressed in human embryonic kidney, exhibited defective electrophysiological properties. Although it is possible that this association was coincidental, this observation offers interesting perspectives about the genetic-environment interaction in relation to an autoimmune-mediated brain disorder.

Most drugs have proven ineffective in DS; with the exception of two randomized class I trials that demonstrated the efficacy of combination treatment with stiripentol, valproate and clobazam,\textsuperscript{32,33} only personal experiences and anecdotic evidence is available. Valproic acid, benzodiazepines, topiramate and levetiracetam have demonstrated some efficacy.\textsuperscript{2} Phenytoin, carbamazepine and lamotrigine can worsen seizures and should be avoided.\textsuperscript{2,34} Prospective studies will clarify to what extent earlier diagnosis and efforts at seizure control will influence clinical deterioration.

Disclosures

The author declares to have no conflict of interest to disclose.

REFERENCES


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