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DRAVET SYNDROME (SEVERE MYOCLONIC EPILEPSY OF INFANCY)

G. Pahlavan

Centro de Investigación en Salud Internacional de Barcelona (CRESIB), Hospital Clínic, 08026 Barcelona, Spain

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ABSTRACT

Dravet syndrome, or severe myoclonic epilepsy of infancy (SMEI), is an intractable epileptic encephalopathy first described by Dravet in 1978. It is characterized by fever-sensitive and refractory generalized clonic, tonic–clonic or unilateral seizures that occur during the first year of life, followed by intractable epilepsy, psychomotor impairment and ataxia. Developmental outcome is poor, with a high mortality rate in childhood. Mutations of the neuronal voltage-gated sodium channel protein type 1 subunit alpha (SCN1A) gene encoding $Na_v1.1$ have been identified as the most frequent genetic cause for the spectrum of genetic and febrile sodium channel epilepsies. Disease penetration has been shown to be highly dependent on parental genetic background, underscoring the importance of genetic counseling. This review will present the latest advances in the genetic characterization of Dravet syndrome, as well as the current disease management strategies.

INTRODUCTION

Severe myoclonic epilepsy of infancy (SMEI) is a distinct epilepsy syndrome first described by Dravet in 1978 (1). The syndrome was so termed in 1981 and clinical diagnostic criteria were established in 1984. The eponym Dravet syndrome (DS) was adopted by the International League Against Epilepsy after atypical cases without myoclonic seizures were documented (2).

Dravet syndrome begins in children under 1 year of age, who develop normally before disease onset. The first seizure, unilateral or generalized tonic–clinic or clonic, is usually associated with fever and subsequently followed by additional generalized and partial seizures, progressing to prolonged, clustered or continuous seizures and to status epilepticus. After the second year of life, patients develop psychomotor delay, ataxia and cognitive impairment. The long-term outcome is unfavorable due to the lack of efficacy of antepileptic drug therapy (3).

Mutations of the neuronal voltage-gated sodium channel protein type 1 subunit alpha (*SCN1A*) gene encoding $Na_v1.1$ have been identified as the most frequent genetic cause for the spectrum of genetic and febrile sodium channel epilepsies, Dravet syndrome being the most severe and malignant form. More than 300 *SCN1A* mutations have been identified to date (4-7), with a predominance of de novo mutations among those studied (8).

The prevalence of this rare disorder is around 6% of the epilepsies that start before 3 years of age, whereas the incidence ranges between 1 per 2000 to 1 per 40,000 children (9), although the incidence may be greater as new genetic evidence is discovered.

DIAGNOSIS

The age dependence of DS symptoms hampers definitive early diagnosis before disease onset. Currently, DS is diagnosed at 2-4 years of age after the appearance of all clinical features. Clinical diagnosis is based on the combination of: 1) early-age onset (< 1 year); 2) occurrence of hemiclonic or generalized tonic–clonic seizures; 3) duration of seizure episodes, which tend to be more prolonged and frequent; 4) impaired psychomotor development; and 5) poor response to antiepileptic drugs. The diagnosis can be established by the occurrence of myoclonic jerks or photically induced spike waves. In the case of atypical absences, partial seizures and obtundation status without myoclonias, the diagnosis is also DS (10-12). Hyperthermia, a major triggering factor even when the temperature is not very high, has high diagnostic value (11, 13). There have been reports associating vaccination with DS onset (14). DS could be retrospectively diagnosed in these cases of alleged vaccine encephalopathy by positive screening of associated *SCN1A* mutations (15, 16).

Dravet syndrome is not associated with previous brain pathology. Patients with DS present normal electroencephalograms initially, which will deteriorate with background activity and the development of frequent generalized abnormalities such as spikes, spike waves, polyspikes and slow waves. Around 50% of patients present photosensitivity during their first year (3, 13). Neuroimaging data by MRI have shown that structural abnormalities, although absent at disease

onset, develop with the occurrence of prolonged febrile convulsions (PFCs) during the course of the disease (17). Reports of the occurrence of hippocampal sclerosis associated with PFCs in patients require further follow-up studies with sourcing of accurate early history (17, 18).

Recently, a screening test before the first year based on early clinical criteria and *SCN1A* mutation analysis has been proposed to help distinguish between DS and benign febrile seizures (19). Moreover, highly sensitive sequencing technology is revealing the nature and breadth of the mutations, which have been shown to go beyond *SCN1A* to adjacent genes (20), as well as balanced translocation disrupting the *SCN1A* gene (21). Successful early screening of DS and associated *SCN1A*-associated diseases depends highly on the development of mutation detection techniques, as well as the study of family genetic background.

GENETICS AND PATHOGENESIS

Over the past 10 years, mutations in voltage-gated sodium channels have become closely associated with epileptic disorders. These channels play a crucial role in the generation and propagation of action potentials (22). Autosomal-dominant heterozygous mutations of the *SCN1A* gene encoding $Na_v1.1$ have been reported in the spectrum of childhood epilepsies including milder generalized epilepsy with febrile seizure + (GEFS+), borderline SMEI (SMEB), intractable childhood epilepsy with generalized tonic–clonic seizures (ICEGTC) and DS, which is the most severe and intractable form of *SCN1A*-associated epileptic disorders (23-25). These observations suggest that SMEI, SMEB and ICEGTC may be genetically related disorders, a hypothesis that requires further genotype–phenotype correlations and the elucidation of the molecular mechanisms involved.

FS ←GFS+ — ICEGTC — SMEB→ DS

The clinical spectrum of *SNC1A*-associated childhood epilepsies

Between 40 and 70% of patients have been shown to carry mutations in $Na_v1.1$ (8, 26, 27), and to date, more than 300 mutations have been associated with DS and related conditions (5-7, 28). Approximately 50% of these mutations are truncating, and the rest include missense, splice-site and deletion mutations (8, 23, 28, 29). Approximately one-third of the mutations are missense, with no predictable effect on channel function (4, 5, 30, 31). The majority of mutations arise de novo (> 80%), but appear to depend strongly on parental background. Germline and somatic mutational mosaicism has been reported in unaffected or mildly affected parents of patients with DS (32-34), underscoring the importance of both genetic screening and counseling.

Intragenic or whole-gene *SCN1A* deletions (35-37), microchromosomal deletions in *SCN1A* and adjacent genes (20), as well as balanced translocation disrupting the *SCN1A* gene (21), have been recently reported in patients with DS without previous mutation records. The sensitivity of the quantitative and qualitative methods used for screening DS appears to be a limiting factor for its genetic characterization. Genetic abnormalities in DS patients need to be sought by techniques such as multiplex ligation-dependent probe amplification or equivalent technologies capable of detecting microdeletions and chromosomal rearrangements in order to establish the correct diagnosis, optimize antiepileptic therapy and provide adequate genetic counseling.

Although reports confirm *SCN1A* deletions as the major genetic cause of DS, the electrophysiological background has not yet been fully elucidated. Whole-cell voltage-clamp recording of panels of SMEI-associated *SNC1A* mutations explored in heterologous systems expressing recombinant *SCN1A* have shown that many, but not all, alleles produce nonfunctional channels, supporting that SMEI stems from functional hemizygosity for *SCN1A*. However, the notion that gain-of-function mutations are associated with GEFS+, and nonfunctional mutations with the more severe disorder DS appears to be an oversimplification, as nonfunctional and gain-of-function *SCN1A* alleles have been described in both cases (25, 38-41). These data suggest that either gain or loss of sodium channel function and either increased or decreased neuronal excitability can cause epilepsy.

MOUSE MODELS OF DRAVET SYNDROME

The observation that loss of voltage-gated sodium channel function may lead to an increase in network hyperexcitability has been explored in $Na_v1.1$-deficient mouse models. The *Scn1a* gene knockout models were characterized by epilepsy with reduced excitability of GABAergic neurons in the hippocampus (42) and GABAergic cerebellar Purkinje cells (43). These findings suggest that $Na_v1.1$ is a predominant sodium channel subtype in at least these two types of brain inhibitory neurons. A similar phenotype was observed in a knock-in mouse model carrying a truncation mutation in the *Scn1a* gene identical to a human DS-associated mutation (44).

Data from these models connect the loss of $Na_v1.1$ in SMEI with impairment of GABAergic neurotransmission in other forms of inherited epilepsy. The deletion of $Na_v1.1$ may alter GABAergic output of inhibitory interneurons by decreasing their whole-cell sodium currents without affecting sodium currents in excitatory pyramidal cells. Decreased sodium current in interneurons may decrease their ability for sustained action potential firing, and by reducing their GABAergic output, enhance the excitability of their downstream synaptic targets.

MANAGEMENT

The treatment of DS is challenging due to its refractory nature and aggravation of epilepsy by the inappropriate use of antiepileptic drugs. The acceleration of cognitive deterioration following seizures makes seizure control crucial to improve prognosis. Current treatments (Table I) are based on the use of maintenance antiepileptic drug therapy, control of hyperthermia, prevention of infectious diseases and treatment with benzodiazepines (3, 13, 45, 46). Generally, two or more broad-spectrum antiepileptic drugs, such as valproate and topiramate, are used at conventional doses (3, 46-48). Enhancement of GABAergic transmission by treatment with clonazepam or other benzodiazepines is standard therapy for epilepsy and is effective in the acute treatment of DS (49). Combination treatment with stiripentol, valproate and clobazam has shown efficacy for the treatment of refractory generalized tonic–clonic seizures in patients with DS (49, 50). Preliminary data using levetiracetam (51, 52), zonisamide (53), bromides (54), immunoglobulin (3) and a ketogenic diet (55, 56) have also indicated positive results

Dravet syndrome patients are refractory to therapy with the sodium channel-blocking anticonvulsant lamotrigine (57). Cases of treat-

Table I. *Current therapeutic management of Dravet syndrome.*

Indication	Treatment	Reference
Fever prevention and treatment	Benzodiazepines: clobazam, clobazepam, diazepam	3, 13, 45, 46
Chronic seizure management	Valproate	3, 46
	Stiripentol	50, 51
	Topiramate	47, 48
	Clobazam	49, 50
	Benzodiazepines (oral)	3, 13, 45, 46
	Levetiracetam	51, 52
	Phenobarbital	60
	Ethosuximide	61
	Zonisamide	53
	Bromide	54
	Ketogenic diet	55, 56
	Immunoglobulin	3

ment with carbamazepine, phenytoin or lamotrigine have resulted in exacerbation of myoclonic and atypical absence seizures (3, 58).

A recent meta-analysis of the literature on available treatments for DS, with a specific analysis of stiripentol efficacy, underscored the importance of randomized, controlled monotherapy trials for the evaluation of new antiepileptic drug treatments (45).

DISEASE OUTCOME

The long-term outcome of DS is unfavorable due to the lack of efficacy of antiepileptic drug therapy. Infancy is dominated by intractable seizures and developmental outcome is poor (3, 13). The risk of sudden death is higher in patients with DS (16%) than in patients of the same age with other epilepsies (5%). Adult diagnosis and long-term clinical findings on the development of patients who survive into adulthood are limited to heterogeneous seizure types with predominant nocturnal generalized tonic–clonic seizures, mild to severe intellectual disabilities and variable motor disabilities (59).

Early diagnosis, although in its early stages, could be made by *SCN1A* genetic testing to allow early implementation of treatment and improvement in cognitive outcome.

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