Child Neurology: Dravet syndrome

When to suspect the diagnosis

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ABSTRACT

Dravet syndrome (DS), previously known as severe myoclonic epilepsy in infancy (SMEI), is an epileptic encephalopathy that presents with prolonged seizures in the first year of life. The seizures often occur with fever or illness, and are frequently initially categorized as febrile seizures. The correct diagnosis of DS and appropriate follow-up are typically delayed. The EEG is normal at onset, and neuroimaging reveals no structural lesion. Early development is normal, but signs of regression appear in the second year of life and are often accompanied by convulsive status epilepticus, alternating hemiconvulsions, and myoclonic seizures. Diagnosis can be confirmed by genetic testing that is now available, and shows mutations within the *SCN1A* gene. Early recognition and diagnosis of DS and management with appropriate anticonvulsants and treatment plan may reduce the seizure burden and improve long-term developmental outcome. *Neurology*® 2009; 73:e59–e62

GLOSSARY

BME = benign myoclonic epilepsy; **DS** = Dravet syndrome; **ED** = epileptiform discharges; **FS** = febrile seizures; **ILAE** = International League Against Epilepsy; **LGS** = Lennox-Gastaut syndrome; **MAE** = myoclonic-astatic epilepsy; **SIMFE** = severe infantile multifocal epilepsy; **SMEB** = borderline severe myoclonic epilepsy; **SMEI** = severe myoclonic epilepsy in infancy.

Severe myoclonic epilepsy in infancy (SMEI) was first described by Dravet in 1982 and was added to the International League Against Epilepsy (ILAE) classification in 1989.^{1,2} “Dravet syndrome” (DS), proposed in the 2001 ILAE report, encompassed SMEI and “borderline” SMEI (SMEB).² SMEB represents SMEI with less frequent seizures and atypical features.^{1–5} The discovery of associated specific mutations within the *SCN1A* gene, in 2001, sparked an interest in DS among pediatric epileptologists.⁶ Outside specialty circles, however, DS remains relatively unknown. This review should increase the index of suspicion for DS among neurologists in training and practitioners.

CLINICAL CASE An 8-month-old girl presented with a right-sided hemiconvulsion without alteration of consciousness for 40 minutes. She was previously healthy, except for recent symptoms of upper respiratory infection. She was born as twin B at 37 weeks' gestation without complications. Her family history was remarkable for a maternal cousin with benign childhood occipital epilepsy. There was no fever, and general and neurologic examinations were normal. Results of serum studies, brain MRI, and routine EEG were normal. The parents were counseled regarding status epilepticus and rectal diazepam prescribed.

At age 11 months, she had a right-sided hemiconvulsion for 22 minutes refractory to rectal diazepam. Days later, she had a prolonged left-sided hemiconvulsion, followed by Todd paralysis. Levetiracetam was initiated. Alternating hemiconvulsions or generalized convulsions occurred 1 to 2 per month despite escalating doses of the anticonvulsant. Triggers for seizures included fever, illness, vaccinations, sleep deprivation, and missed medication doses. Overnight video EEG monitoring at age 13 months revealed polymorphic right-sided frontocentral spikes maximal during sleep, and asymmetry of the posterior dominant rhythm. At age 18 months, she presented in status epilepticus refractory to 2 doses of rectal diazepam and fosphenytoin. Valproic acid was added. At age 2 years, she has normal development and neurologic examination and has not

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Table Differential diagnosis of Dravet syndrome ^{1,3,4}						
Clinical feature	DS	FS	SIMFE	BME	LGS	MAE
Onset <1 y	+	+/-	+/-	+/-	-	-
Fever-sensitive seizures	+	+	+/-	-	-	+/-
Hemiconvulsion	+	-	+/-	-	-	-
Generalized convulsion	+	+/-	+/-	-	+/-	+
Partial seizures	+	+/-	+	-	+/-	-
Myoclonic seizures	+/-	-	-	+	+/-	+
Tonic seizures	-	+/-	-	-	+	-
Atypical absence seizures	+/-	-	-	-	+	+
Generalized ED	+/-	-	-	+	+	+
Multifocal ED	+/-	-	+	-	-	-
Photosensitivity	+	-	-	-	-	-
Abnormal development	+	-	+	-	+	+
Abnormal brain MRI	-	-	-	-	+/-	-

DS = Dravet syndrome; FS = febrile seizures; SIMFE = severe infantile multifocal epilepsy; BME = benign myoclonic epilepsy; LGS = Lennox-Gastaut syndrome; MAE = myoclonic astatic epilepsy; ED = epileptiform discharges; + = usually present; +/- = maybe present; - = usually absent.

experienced any unprovoked seizures during valproate monotherapy.

Differential diagnosis. The first episode of convulsive focal status epilepticus in an otherwise normal infant with normal neuroimaging has many potential etiologies. Children with DS are frequently initially diagnosed with febrile seizures or febrile status epilepticus.^{1,3} Focal epilepsy due to an occult structural lesion should be excluded by serial neuroimaging. Subsequent alternating hemiconvulsions make a structural lesion improbable in our patient. Progressive myoclonic epilepsies due to metabolic disorders, such as neuronal ceroid lipofuscinosis, are excluded by the absence of typical clinical features.^{1,3} Family history of benign childhood occipital epilepsy in our patient supported the initial diagnosis of idiopathic focal epilepsy at presentation.

The differential diagnosis of DS includes severe infantile multifocal epilepsy (SIMFE), benign myoclonic epilepsy (BME), Lennox-Gastaut syndrome (LGS), and myoclonic-astatic epilepsy (MAE).^{1,3} (table) SIMFE is a severe variant of cryptogenic focal epilepsy, not listed by ILAE, with onset in the first year of life, multiple seizure types including complex partial and hemiconvulsive, and multifocal epileptiform discharges. Unlike DS, SIMFE does not exhibit myoclonic seizures, absence seizures, or generalized epileptiform discharges. Developmental regression has a later onset, but with the same poor long-term outcome.⁴ Our patient has characteristics of SIMFE. BME is excluded by the presence of other seizure types and an abnormal EEG. LGS has a later onset, seizures that are more tonic and atonic, and slow

spike and wave on EEG. MAE may have an onset similar to DS but is differentiated by the eventual presence of drop attacks.^{1,3} *SCN1A* mutations can be present in these epileptic encephalopathies.⁴

Given this clinical course, DS was suspected, and DNA sequence analysis of the *SCN1A* gene showed a de novo (parental testing negative) frameshift mutation (deletion GTTT at nucleotide position 5010–5013 at codon 1670) that is previously reported with the classic SMEI phenotype.⁶ The lack of myoclonic seizures or multifocal epileptiform discharges suggests that our patient's condition is best classified as a borderline variant of DS, previously known as SMEB.^{3,5}

DISCUSSION Epidemiology. DS is found in 1 per 20,000 to 1 per 40,000 members of the population, with a male-to-female ratio of 2 to 1. Three percent to 8% of patients with their first seizure before age 1 year have DS.³

Clinical characteristics. Diagnosis is based on age at onset, seizure types, and clinical course. Seizures begin in the first year of life in all cases, followed by a variable course that includes different seizure types, developmental regression, and seizure intractability. Certain typical features are required for DS, whereas other manifestations are more variable, leading to the expansion of the syndrome to include SMEB.^{1,3,5,7}

The first seizure occurs at 5 to 6 months of age, with a range of 2 to 10 months, and is characterized by a generalized or unilateral convulsion.^{1,3} Early seizures are typically prolonged and associated with fever or infection. By age 2 years, polymorphic seizure semiology emerges and may include focal and generalized myoclonus, atypical absence, complex partial (atonic, autonomic, automatisms), and “obtundation status.” Obtundation status is a special seizure type in DS and consists of fluctuating alteration of consciousness with reduced postural tone and myoclonic jerks. Seizure triggers include fever, infectious illness, increased body temperature (e.g., hot bath water), and photic or pattern stimulation.^{3,5}

Development is always normal at onset, with a plateau and progressive decline between 1 and 4 years of age, typically in the second year of life.³ The degree of neurobehavioral impairment is reported to range from minor learning difficulty to global developmental delay.⁸ Patients with SMEB have a slightly better developmental outcome.⁵ Ataxia and increased reflexes are sometimes found, but their presence is not necessary for diagnosis.³

Genetics. Family history of epilepsy or febrile seizures is reported in approximately 25% of cases.³ Mutations within the gene for the α subunit of the

voltage-gated sodium channel 1.1, SCN1A, are found in 67% to 86% of patients from larger studies with DS (SMEI and SMEB) and 5% to 11.5% of those with generalized epilepsy with febrile seizures plus.^{3,4,7,8} In a recent report of 359 different SCN1A mutations, DS was the most common (86%) associated phenotype.⁹ Mutations are found with other epilepsies, nonepileptic disorders, and febrile seizures.^{4,9} SMEI is sometimes considered the severe form of a continuous spectrum associated with the SCN1A.^{3,4} Mutations found in classic SMEI patients were previously reported with a cryptogenic focal epilepsy phenotype.^{4,7} Most mutations occur de novo, but inherited cases and parental mosaicism are also described.^{3,4,6,7} Because approximately 20% of DS patients do not have a detectable SCN1A mutation, the significance of mutations in other genes will need to be determined.^{3,7,9,10}

Pathogenesis. The voltage-gated sodium channel is responsible for the initiation of action potentials and, therefore, is involved in neuronal excitability.^{3,4,6,7,9,10} The α subunit has 4 homologous domains, with 6 transmembrane segments each, that form the voltage sensor and ion-conducting pore.¹⁰ Mutations cause either a gain or a loss of function.⁹ Initially, researchers could not explain how loss-of-function mutations could lead to seizures. A mouse model of DS showed selective loss of sodium current in the hippocampal γ -aminobutyric acid-mediated inhibitory interneurons. Failure of inhibition leading to excitation is a proposed pathogenesis of this mutation in DS.¹⁰

Diagnosis. The clinical diagnosis is supported by EEG, neuroimaging, and *SCN1A* mutation.³ EEG is typically normal at onset, but often progresses to generalized spike-and-wave discharges. Like the seizure semiology, a variety of interictal EEG findings is more common.^{1,3,5,8} Some patients may have persistently normal interictal records.⁸ Neuroimaging is normal. In the United States, testing for *SCN1A* is commercially available. Athena Diagnostics Inc. (Worcester, MA) offers DNA sequencing to detect mutations within the coding regions and multiplex ligation-dependent probe amplification to uncover genomic deletions/duplications. Transgenomic Molecular Laboratory (Omaha, NE) scans for mutations with denaturing high-performance liquid chromatography, and then abnormal profiles are subjected to DNA sequencing. Parents are tested to establish inheritance and clinical significance.

Treatment. Intractable seizures are a hallmark of DS. Experience with carbamazepine and lamotrigine in DS show exacerbation of seizures and should be avoided.³ Efficacy of other anticonvulsants is variable. Valproate and topiramate are the most promis-

ing agents available in the United States; levetiracetam is also used.^{3,8} In Europe, stiripentol, an inhibitor of cytochrome P450, is added to the combination of valproate and clobazam and is particularly effective against status epilepticus.³ Ketogenic diet is another option.^{3,8}

Counseling regarding avoidance of triggers is very important. Preventive measures include avoiding hot baths or using cooling vests in hot weather if hyperthermia sensitive, or wearing sunglasses if photosensitive. Emergency benzodiazepine should be used in the home to prevent status epilepticus. Resources for parents are available from the International Dravet syndrome Epilepsy Action League (www.idea-league.org).

Prognosis. Outcome is poor and, after 4 years of age, patients usually reach a steady state of intractable seizures, intellectual impairment, behavioral disorders, and neurologic abnormalities. Myoclonic seizures usually cease and are replaced with nocturnal generalized clonic or absence seizures.³ The number of seizures is a risk factor for the degree of developmental regression. The mortality rate is approximately 16% and is related to prolonged convulsive seizures, drowning, and sudden unexpected death.³

CONCLUSIONS DS is a severe epileptic encephalopathy that is difficult to recognize at the time of onset. Early recognition and diagnosis of DS and management with appropriate anticonvulsants and treatment plan may reduce the seizure burden and improve long-term developmental outcome. The diagnosis should also be considered in adults with infantile-onset refractory epilepsy, by reevaluation of childhood history and *SCN1A* testing.

DISCLOSURE

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