Brain & Development 38 (2016) 40–46

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Efficacy of antiepileptic drugs for the treatment of Dravet syndrome with different genotypes

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Received 8 October 2014; received in revised form 28 June 2015; accepted 30 June 2015

Abstract

Objective: Evaluation of the efficacy of antiepileptic drugs (AEDs) used in the treatment of Dravet syndrome (DS) with different genotypes.

Methods: Patients with DS were recruited from different tertiary hospitals. Using a direct sequencing method and Multiplex Ligation-Dependent Probe Amplification (MLPA), genetic abnormalities were assessed within the exons and flanking introns of *SCN1A* gene, which encodes the α1 subunit of neuronal sodium channels. Patients were divided into *SCN1A*-positive and *SCN1A*-negative groups according to the results of genetic tests. Medical records, including detailed treatment information, were surveyed to compare the effect of different AEDs on clonic or tonic–clonic seizures (GTCS). Efficacy variable was responder rate with regard to seizure reduction.

Results: One hundred and sixty of 276 (57.97%) patients had mutation in *SCN1A* gene (only 128 of them had provided detailed medical records). Among the 116 patients without *SCN1A* mutations, 87 had provided detailed medical records. Both older AEDs (valproate, phenobarbital, bromide, carbamazepine, clonazepam, and clobazam) and newer AEDs such as zonisamide were used in these patients. Valproate was the most frequently used AED (86.72% in the *SCN1A*-positive group, 78.16% in the *SCN1A*-negative group), with 52.25% and 41.18% responder rates in *SCN1A*-positive and *SCN1A*-negative patients, respectively ($P = 0.15$). Bromide was used in 40.63% of the *SCN1A*-positive patients and 20.69% of the *SCN1A*-negative patients, and its responder rates were 71.15% and 94.44% in *SCN1A*-positive and *SCN1A*-negative patients, respectively ($P = 0.05$). Efficacy rates of clonazepam, clobazam, phenobarbital, and zonisamide ranged from 30% to 50%, and these rates were not correlated with different genotypes ($P > 0.05$). Carbamazepine had either no effect or aggravated seizures in all *SCN1A*-positive patients.

Significance: Bromide is most effective and is a well-tolerated drug among DS patients, especially among *SCN1A*-negative patients. Carbamazepine should be avoided in patients with *SCN1A* mutations.

Keywords: Genetic tests; Dravet syndrome; Antiepileptic drug therapy; Efficacy

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http://dx.doi.org/10.1016/j.braindev.2015.06.008
0387-7604/

1. Introduction

Dravet syndrome (DS) is a rare and malignant epileptic syndrome with a reported incidence of between 1 per 20,000 [1] and 1 per 40,000 children [2]. DS usually develops in the first year of life [3] and is now considered as a disease entity that includes severe myoclonic epilepsy during infancy (SMEI) and severe myoclonic epilepsy-borderline (SMEB) [4]. Patients initially present with recurrent and prolonged seizures, which are usually febrile, hemiclonic, or generalized tonic clonic; frequently, these seizures result in status epilepticus (SE). As patients age, their clinical features evolve into a variety of afebrile or fever-induced seizure types. Cognitive outcome is poor, with a high risk of psychomotor retardation. Heterozygous *SCN1A* mutations and micro-chromosomal deletions involving *SCN1A* have been reported as the major cause of DS.

Although *SCN1A* mutations are the major cause of DS, no preventative therapies have yet been developed. Until recently, therapy for DS consisted mainly of avoiding seizure triggers (e.g., hyperthermia, illness, stress, flickering lights, and temperature change), implementing a strict, aggressive and acute seizure management protocol, and using a low-dose drug maintenance treatment. In general, conventional drug treatments are unsatisfactory; therefore, a combination of old AEDs (valproate [VPA], clonazepam [CZP], and clobazam [CLB]) and new AEDs (topiramate [TPM] and stiripentol [STP]) is recommended [5,6]. For example, Kassai et al. [7] performed a systematic review of the literature, and reported that STP concomitant with CLB and VPA can greatly reduce seizure frequency after 2 months of treatment. Recently, Ceulemans et al. [8] reported that 70% of patients with DS are seizure-free with fenfluramine as an add-on treatment to STP. STP and fenfluramine are currently available in only a limited number of countries; in Japan, where most new AEDs have not been available until recently, DS treatment has posed a significant challenge to child neurologists.

Ceulemans et al. have proposed guidelines for the optimal treatment of DS with *SCN1A* mutations [5]. Their approach includes a maintenance treatment based on a combination of only 2 AEDs (VPA and TPM). Unfortunately, only 12 participants were included in their study; indeed, most studies, evaluating the efficacy of AEDs, have included relatively few participants. The limited number of patients in previous studies and the severity of this syndrome justify the necessity for providing informative knowledge about the best treatment practices for this condition. Therefore, we performed a retrospective study to survey the efficacy of AEDs in DS with different genotypes.

2. Methods

2.1. Patients

This study includes 276 patients diagnosed with DS (SMEI, $n = 219$; SMEB, $n = 57$) at child neurology departments in various regional tertiary hospitals. The diagnoses of SMEI and SMEB were made according to the proposal of the Commission on Classification and Terminology of the International League Against Epilepsy and the following criteria: (a) high incidence of family history of epilepsy or febrile convulsions; (b) normal physical and neurologic development before onset; (c) appearance of seizures during the first year of life in the form of generalized or unilateral febrile and afebrile clonic seizures, secondary appearance of myoclonic jerks, and often partial seizures; (d) no paroxysmal discharge on the electroencephalogram (EEG) in the early stages, but possible subsequent appearance of generalized spike-waves, polyspike-waves, and focal abnormalities; with possible early appearance of photosensitivity (although rare, paroxysmal discharge may appear in the first recordings); (e) normal psychomotor development initially, but retardation evident from the second year of life, together with the appearance of ataxia, pyramidal signs, and interictal myoclonus; and (f) all seizure types are resistant to every form of treatment [9]. SMEI diagnosis was based on fulfillment of all the accepted diagnostic criteria for SMEI [10], whereas SMEB diagnosis was based on the presence of clinical features almost identical to those of SMEI, but excluding myoclonic and atypical absence seizures. Each participant or their parent/guardian signed an informed consent form approved either by the Ethics Review Committee of Fukuoka University or by ethics review committees of the other participating institutions.

2.2. Genetic analysis

Genomic DNAs were prepared from ethylenediaminetetraacetic acid (EDTA)-treated whole-blood samples using a QIAamp DNA Blood Kit (Qiagen, Hilden, Germany). *SCN1A* was screened for genetic abnormalities using a direct sequencing method with an automatic sequencer. Multiplex Ligation-Dependent Probe Amplification (MLPA) tests, conducted according to the manufacturer's protocol, were performed on patients without mutations using a commercially available kit for *SCN1A* (SALSA MLPA KIT P137 SCN1A, Lot 0107 or Lot 0805, MRC-Holland, Amsterdam, the Netherlands). Details of the PCR conditions and the primers used are available upon request. Reference sequences of messenger RNA (mRNA) were based on information available