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Original article

Dravet syndrome: Early clinical manifestations and cognitive outcome in 37 Italian patients

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Abstract

Aims of our study were to describe the early clinical features of Dravet syndrome (SMEI) and the neurological, cognitive and behavioral outcome. The clinical history of 37 patients with clinical diagnosis of SMEI, associated with a point mutation of SCN1A gene in 84% of cases, were reviewed with particular attention to the symptoms of onset. All the patients received at least one formal cognitive and behavior evaluation. Epilepsy started at a mean age of 5.7 months; the onset was marked by isolated seizure in 25 infants, and by status epilepticus in 12; the first seizure had been triggered by fever, mostly of low degree in 22 infants; the first EEG was normal in all cases. During the second year of life difficult-to-treat seizures recurred, mostly triggered by fever, hot bath, and intermittent lights and delay in psychomotor development became evident. At the last evaluation, performed at a mean age of 16 ± 6.9 years, mental retardation was present in 33 patients, associated with behavior disorders in 21. Our data indicate that the most striking features of SMEI are: the early onset of seizures in a previously healthy child, the long duration of the first seizure, the presence of focal ictal symptoms, and sensitivity to low-grade fever. Diagnosis of SMEI may be proposed by the end of the first year of life, and a definite diagnosis can be established during the second year based on the peculiar seizure-favoring factors, EEG photosensitivity and psychomotor slowing. The temporal correlation between high seizure frequency and cognitive impairment support the role of epilepsy in the clinical outcome, even if a role of channelopathy cannot be ruled out.

Keywords: Dravet syndrome; SCN1A; Epileptic encephalopathy; Diagnosis; Mental retardation

1. Introduction

Severe myoclonic epilepsy in infancy (SMEI) is an epileptic encephalopathy [1], in most cases associated with a de novo mutation of the SCN1A gene, which encodes the voltage-gated sodium channel Nav1.1 [2,3]. The disease starts in the first year of life and is characterized by febrile or afebrile seizures. During the second year of life, the clinical picture is enriched by the occurrence of polymorphic seizures [4,5]. Though the early recognition of the syndrome is crucial for an appropriate management and focused treatment, the diagnosis is often delayed after the age of 3 when all the electroclinical features of the syndrome become evident [6].

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Most patients, all seemingly normal before seizures onset, exhibit delayed psychomotor development, cognitive impairment and behavioral disorders since the second–third year of life, after prolonged, drug resistant convulsive seizures have appeared [7].

Aims of our study were (a) to identify the early clinical manifestations of SMEI that can prompt an early diagnosis, genetic investigation and targeted treatment. (b) To evaluate the neurological, cognitive and behavior outcome to contribute in understanding the respective roles of epilepsy and of the genetic background in influencing patients outcome.

2. Patients and methods

The case series consists of 37 patients (16 males and 21 females), including two siblings (cases 5 and 6) that met the clinical diagnostic criteria of SMEI according to the ILAE classification [8]; only patients whose clinical history and laboratory data were available from the onset were enrolled. Given the characteristics of our Centres, two tertiary centres in northern Italy, most patients have been evaluated a few years after seizure onset, and only 12 within the first year of life. In all cases, however, the clinical histories were analyzed with particular attention to family histories, the presence of risk factors for brain damage, motor, mental and speech development. A detailed history of epilepsy was collected focusing on modality of seizure onset, according to the following items: age, presence and degree of fever, semeiology of the first seizure, presence of focal or lateralized symptoms, and duration. Seizures lasting more than 10 min were defined as prolonged, whereas the term status was reserved for seizures lasting more than 30 min. As far as the disease course, particular attention was given to the semeiology and frequency of subsequent seizures, triggering factors and recurrence of status epilepticus.

At the first our evaluation, performed at a mean age of 5.6 ± 5.5 years (4 months–21 years), all the patients underwent neurological examination, cognitive assessment (by Griffiths's Scale, Wechsler or clinical observation, according to the age and level of collaboration) and behavior observation. Wake and sleep EEG with video and polymyographic monitoring was obtained in all patients, and MRI in all but one. The age at the last evaluation ranged between 6 months and 28 years (mean 16 years). Twenty-three patients have been longitudinally followed-up for a mean period of 6.3 years (6 months–18 years) by serial clinical and EEG examinations, and standardized cognitive assessment.

Alpha-subunit type A of voltage-gated sodium channel (SCN1A) mutational screening was performed by DHPLC and multiplex ligation probe amplification (MLPA) in all patients.

Clinical and genetic scores aimed at screening SMEI in the first year of life, as recently proposed [9] were calculated in all cases with the exception of a single child for whom information on the first year were not completely available.

3. Results

3.1. Family history

A positive family history for seizures was reported in 16 patients, i.e. 46% of the 35 with a known familial history: epilepsy was reported in first or second degree relatives in seven patients, febrile convulsions in three, and both epilepsy and febrile convulsions in six patients, epilepsy in most cases was in the form of idiopathic generalized syndromes.

3.2. Personal history

Personal risk factors were reported in 15 cases, including: threatened miscarriage 4 patients; neonatal respiratory distress, 4; gestosis, 2; intrauterine growth retardation, 2; polyhydramnios, 1; two patients were adopted child. The psychomotor development was normal before the onset of seizures in all infants but one who had mild motor developmental delay (case 32).

3.3. Clinical features at onset and during the first year of life

The age at the first seizure ranged between 3 and 11 months (mean: 5.7 ± 2.1), and was within the 6th month of life in 27 (73% of cases). Twenty-two infants (59%) experienced their first seizure during febrile illness, but, notably, only in two cases fever was higher than 38.5 °C. Seizure features at onset are summarized in Table 1; remarkably, the first seizure lasted more than 20 min in 18 patients, and focal signs were reported in 19.

In the 27 patients younger than 6 months, prolonged seizures often marked the onset of epilepsy: status epilepticus was the first symptom in 11 cases and seizures longer than 10 min in a further 7; focal seizures or status mostly occurred without fever (9 cases), whereas generalized seizures were more frequently triggered by high temperature (10 cases). By contrast, the first seizure was brief in most of the 10 infants with onset after the 6th month of life, and only three patients experienced status epilepticus as a first symptom. EEGs at onset were reported to be normal in all cases, regardless the age of onset.

The course of the disease in the first year of life was characterized by: prolonged fits (29 patients), recurrence of focal seizures (15 cases) and hemiconvulsions (14 cases); seizures were favoured by fever or intercurrent illness in most patients, and triggered by hot water in 3; myoclonic seizures appeared within one year of age in two cases (Table 1). Early EEG recordings were available for 21 patients: photosensitivity was evident by the age of 1 in two of these cases (Fig 1A).