Acta Neurol. Belg., 2010, **110**, 281-283

A novel de novo SCN1A missense mutation in Severe Myoclonic Epilepsy Borderland

Nicola Specchio[1], Marina Trivisano[2], Martina Balestri[1], Elena Gennaro[3], Luigi M Specchio[2], Lucia Fusco[1], Federico Zara[4], Federico Vigevano[1]

[1]Division of Neurology, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy
[2]Clinic for Nervous System Diseases, University of Foggia, Foggia, Italy
[3]Laboratory of Genetics, E.O. Ospedali Galliera, Genova, Italy
[4]Muscular and Neurodegenerative Disease Unit, Institute "G. Gaslini", University of Genova, Italy

Abstract

In this report we describe a novel missense SCN1A mutation in a patient affected by Severe Myoclonic Epilepsy Borderland (SMEB). This three and a half year-old female patient experienced prolonged febrile seizures at the age of 14 months, followed by generalized tonic-clonic seizures, atonic seizures, atypical absences almost in a cluster and triggered by fever. Cognitive and motor development was normal. The case was suggestive for SMEB. SCN1A analysis revealed an unknown de novo point mutation: a heterozygous replacement of nucleotide G with nucleotide T in position 4183 of the coding region of the gene (c.4183 G>T) in exon 21. This mutation causes the replacement of aspartic acid with tyrosine in 1395 (p.D1396Y). Even if other SCN1A missense mutations localized in the same region are associated to SMEB, a definite genotype-phenotype correlation has not yet been found, probably because other factors are involved in the pathogenesis of this type of epilepsy.

Keywords: Novel SCN1A mutation, de novo missense mutation, epilepsy, SMEI, SMEB, Dravet Syndrome.

Introduction

The majority of known mutations in SCN1A, the gene encoding the voltage-gated neuronal sodium channel alpha 1 subunit (Nav1.1), lead to severe myoclonic epilepsy in infancy (SMEI; MIM# 607208), with a significant number also accounting for generalized epilepsy with febrile seizures plus (GEFS+; MIM# 604233), borderland SMEI (SMEB) and intractable childhood epilepsy with generalized tonic-clonic seizures (ICEGTCS) (1).

SMEB is characterized by the lack of some clinical features of SMEI such as myoclonic seizures or generalized spike-wave discharges (2). Within SMEB populations, children suffering from generalized tonic-clonic seizures beginning in the first year of life have also been reported; these children do not progress towards other seizure types, and the disease course is less unfavourable than in SMEI patients. SCN1A mutations have been found in 69% of such cases. We report a novel *de novo* missense SCN1A mutation in a patient affected by SMEB.

Case Report

This three and a half year-old female patient was born at term after an uneventful pregnancy and with a physiologic delivery. Neurological examination was normal. Familial history of childhood absence epilepsy and afebrile tonic-clonic generalized seizures was reported. A mathernal second-degree cousin had typical absence seizures from the age of 4 years easily treated with valproate, with no recurrence. A second maternal first-degree cousin at the age of 18 months presented with a prolonged afebrile tonic-clonic seizure with spontaneous remission. He is now 4 years and 6 months old and he never experienced successive seizures. He was not treated. The proband, at the age of 14 months, during sleep, had a prolonged afebrile tonic-clonic generalized seizure. Laboratory tests, sleep EEG and cerebral CT were normal. Two months later, she presented successive atonic seizure and, 24 hours later, she had a febrile tonic-clonic seizure during an episode of otitis. This was followed by a six-month seizure-free period. She then experienced an increasing number of febrile atonic seizures, atypical absences, and focal seizures. All these episodes occurred almost in a cluster and were triggered by fever (also with a very mild increase of temperature) or infections. She also

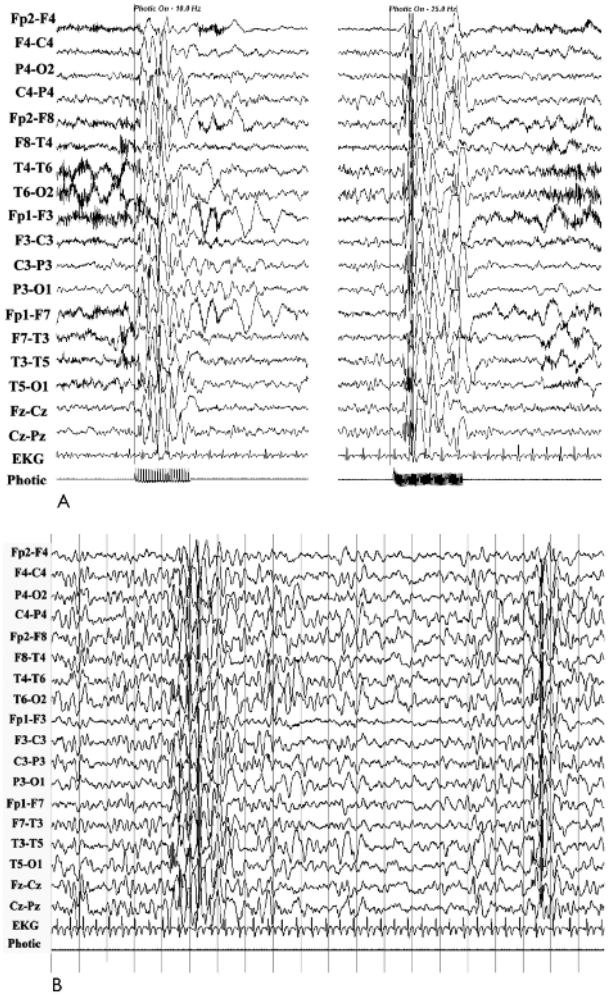

Fig. 1 A.— Intermittent photic stimulation (IPS) showing a photoparoxysmal response (PPR) between the frequencies of 10 Hz to 25 Hz. B. Diffuse poly spikes-and-waves during stage II of N-REM sleep at the age of two years and two months.

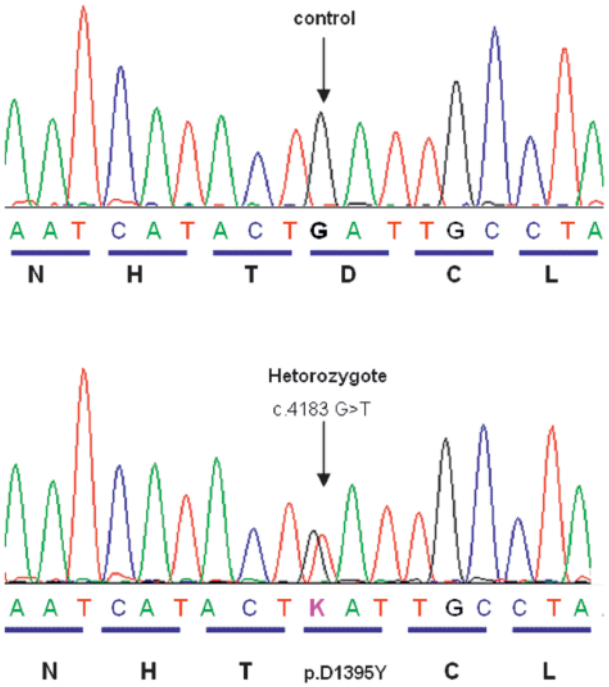

Fig. 2. — Missense mutation identified in our patient. SCN1A gene mutational analysis showed a novel heterozygous point mutation.

experienced a non-convulsive status epilepticus. At the age of two years and two months, diffuse poly spikes-and-waves appeared during sleep (Fig. 1B) together with a photoparoxysmal response between the frequencies of 10-25 Hz (Fig. 1A). She was treated with valproate at a dose of 35 mg/kg/day, with partial reduction of seizures. Myoclonic seizures were never reported.

This case was suggestive for SMEB and mutational analysis for SCN1A was performed. The 26 exons of *SCN1A* (transcript reference AB093548 [GenBank]) were amplified by PCR in 29 fragments from the genomic DNA as described previously (1). Sequence products were run on an automated sequencer (ABI 3730; Applied Biosystems, Foster City, California, USA) and data were analysed with Seqscape V.2.5 software (Applied Biosystems).

An unknown point mutation was found: a heterozygous replacement of nucleotide G with nucleotide T in position 4183 of the coding region of the gene (c.4183 G>T) in exon 21. This point mutation causes a single amino acid change: the replacement of aspartic acid with tyrosine in 1395 (p.D1395Y) (Fig.2). Parents have been tested and the sequence analysis did not reveal the mutation identified in the patient. This was a novel *de novo* missense mutation.

Our patient now takes valproic acid but monthly febrile and afebrile focal and generalized seizures continue to occur. Cognitive development remains normal.

Discussion

SCN1A (MIM# 182389) is the most clinically relevant amongst all the known epilepsy genes, with the largest number of epilepsy-related mutations characterized so far (1). The proportion of patients with SCN1A mutations in a recent series of 333 SMEI patients was 73% (4), and with other more sensitive techniques, a proportion (10-25%) of negative cases were found to carry intragenic deletions or duplications (5). The incidence of the SCN1A mutation in SMEB patients is slightly lower (69%) (1). Amongst the SMEB patients

with SCN1A mutations, 43% have a missense mutation, 43% have a nonsense mutation and 10% a deletion (1).

Our patient has an exonic mutation localized in exon 21 where 14 mutations have already been described. The clinical phenotype of the mutations in this exon is wide and includes patients with SMEI, SMEB and GEFS+ (3). Three of these 14 mutations are associated to SMEB but only one of them is localized in D3/S5 like the mutation we found. This region is important for the control of ion selectivity and permeation. Missense mutations in this region almost always lead to SMEI or SMEB, while a missense mutation in the voltage-sensor S4 region may lead to GEFS+ or SMEI, and mutations outside S4-S5 mostly lead to GEFS+ or SMEB (4). Although hundreds of mutations have been reported in SCN1A gene, in the region D3/S5 of the exon 21 only one was associated with a SMEB phenotype. The clinical features of the only case described in the literature with the SCN1A missense mutation localized in D3/S5 of the exon 21 is characterized by onset before 1 year, absence of both myoclonic seizures and atypical absence, and moderate mental retardation is also reported (2). This is quite different from our patient with age at onset of 14 months, presence of atypical absences and normal cognitive development.

On the one hand this observation strength the concept that there is not a definite genotype-phenotype correlation in SCN1A mutations and other factors would be involved in pathogenesis of this type of epilepsy. On the other hand it is important for clinicians to know if a specific mutation is already associated to a particular phenotype in order to collect more patients with same mutations and better define the wide spectrum of clinical entities with associated to mutations in SCN1A.

REFERENCES

1. Harkin LA, McMahon JM, Iona X, Dibbens L. *et al*. The spectrum of SCN1A-related infantile epileptic encephalopathies. Brain. 2007;130:843-52.
2. Fukuma G, Oguni H, Shirasaka Y. *et al*. Mutations of neuronal voltage-gated Na+ channel alpha 1 subunit gene SCN1A in core severe myoclonic epilepsy in infancy (SMEI) and in borderline SMEI (SMEB). Epilepsia. 2004;45:140-8.
3. Lossin C. A catalog of SCN1A variants. Brain Dev. 2009;31:114-30.
4. Depienne C, Trouillard O, Saint-Martin C. *et al*. Spectrum of SCN1A gene mutations associated with syndrome: analysis of 333 patients. J Med Genet. 2009;46;183-91.
5. Marini C, Scheffer I, Nabbout R. *et al*. SCN1A duplications and deletions detected in Dravet syndrome: Implications for molecular diagnosis. Epilepsia. 2009;50:1670-8.

Nicola Specchio, MD
Division of Neurology
Bambino Gesù Children's Hospital – IRCCS
P.za S. Onofrio, 4 00165 Rome, Italy
e-mail: nicola.specchio@opbg.net