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Case report

Novel *de novo* splice-site mutation of *SCN1A* in a patient with partial epilepsy with febrile seizures plus

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Abstract

This report describes a 4-year-old male patient experienced prolonged febrile seizures after 1 year of age, multiple febrile seizures and complex partial seizures with secondary generalization. The gene encoding voltage-gated sodium channel α1-subunit: *SCN1A* analysis revealed a heterozygous *de novo* one-point mutation (IVS16 + 2 T > C) at a splice-acceptor site. This mutation was inferred to cause truncation of the α1-subunit molecule and, thereby, a loss of channel function. To date, truncation mutation has been found exclusively in patients with severe myoclonic epilepsy in infancy (SMEI), although only missense mutations have been found in generalized epilepsy with febrile seizures plus (GEFS+), partial epilepsy with FS+, FS+, and FS. The patient's phenotype is consistent with that of partial epilepsy with FS+, rather than SMEI, including borderline SMEI (SMEB). We present the first case report of partial epilepsy with FS+ associated with a truncation mutation of *SCN1A*. The possibility exists for concomitant involvement of multiple genes other than *SCN1A* for seizure phenotypes.

Keywords: Novel *SCN1A* mutation; GEFS+ spectrum; Partial epilepsy with FS+; Splice-site mutation; Truncating type mutation

1. Methods

Genomic DNAs were prepared from ethylenediaminetetraacetic acid (EDTA)-treated whole blood samples using QIAamp DNA Blood kit (Qiagen Inc., Hilden, Germany). Screening for genetic abnormalities of *SCN1A*, *SCN2A*, *SCN1B*, and *SCN2B* was performed using a direct sequencing method with an automatic sequencer, as described previously. In brief, primers were designed to amplify all exons and the flanking intronic splice sites of the genes. The purified products of polymerase chain reaction (PCR) were directly sequenced and analyzed using an automated sequencer. Details of the PCR conditions and the primers used are available upon request. Reference sequences of mRNA were based on information available from GenBank (Accession Nos.): Human *SCN1A*, AF117907.1; Human *SCN2A*, M94055. This study was conducted after written informed consent was obtained from the parents.

2. Case

The patient was a 4-year-old boy born to non-consanguineous healthy parents at term with a normal birth

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weight after an uneventful pregnancy. His family history included febrile seizure, epilepsy, and developmental disorders were unremarkable. Physical findings were not remarkable and no ataxia was found. He experienced a prolonged febrile seizure for about 70 min at age 13 months. Electroencephalography (EEG) and brain magnetic resonance imaging (MRI) were normal. At age 15 months, he developed multiple febrile seizures without laterality. Because attempts to prevent febrile seizures using a diazepam suppository had failed, valproate was administered. Valproate did not control multiple febrile seizures completely, but decreased the seizure frequency. His motor milestones in infancy were normal and he walked unaided at age 14 months. However, intellectual disabilities became evident at age 18 months. At age 28 months, EEG revealed sharp waves over the left frontal and temporo-frontal areas (Fig. 1). At 32 months, he developed a right clonic motor seizure without fever, beginning from the right upper limb and propagating to the right lower limb, resulting in generalized tonic–clonic convulsive status epilepticus for 30 min. Brain MRI was normal. Carbamazepine was substituted for valproate; it controlled complex partial seizures, as well as multiple febrile seizures, almost completely. At 40 months of age, his psychomotor developmental quotient was 53 in language and society, 55 in cognition and adaptation. At 11 months after that, his psychomotor developmental quotient had slightly elevated to 59 in language and society, and to 67 in cognition and adaptation.

Mutational analysis for *SCN1A*, *SCN2A*, *SCN1B*, and *SCN2B* revealed a novel heterozygous splice-site point mutation (IVS16 + 2 T > C) of *SCN1A* in the patient. (Fig. 2). The mutation was located at the splice-acceptor site of exon 17 and was deduced to result in an aberrant splicing (Fig. 3). In fact, the splicing expected with the normal sequence at this site was considered to be abolished by the mutation IVS16 + 2 T > C according to the *Alternative Splice Predictor* (ASSP, http://es.embnet.org/~mwang/assp.html). Furthermore, the mutation was not detected in her parents or in 98 healthy volunteers. No mutation was identified within *SCN2A*, *SCN1B*, or *SCN2B*. Consequently, the mutation was considered to be a pathogenic and *de novo* mutation.

3. Discussion

In this report, we describe a patient with a novel splice-site mutation (IVS16 + 2 T > C), which is inferred to have caused a truncation in the *SCN1A* molecule. The phenotype of the patient was more consistent with that of partial epilepsy with FS+ than with SMEI, including borderline SMEI (SMEB).

Now recognized as a common epilepsy syndrome, GEFS+ was first described by Scheffer and Berkovic [1]. As defined, GEFS+ is a heterogeneous epilepsy syndrome that is characterized by febrile seizures (FS) that persist beyond the age of six years, or afebrile seizures exhibiting various phenotypes including generalized epilepsy as well as partial epilepsy [2]. Inheritance of GEFS+ is apparently more complex than simple autosomal dominant inheritance, where GEFS+ is considered to be genetically heterogeneous, and inheritance

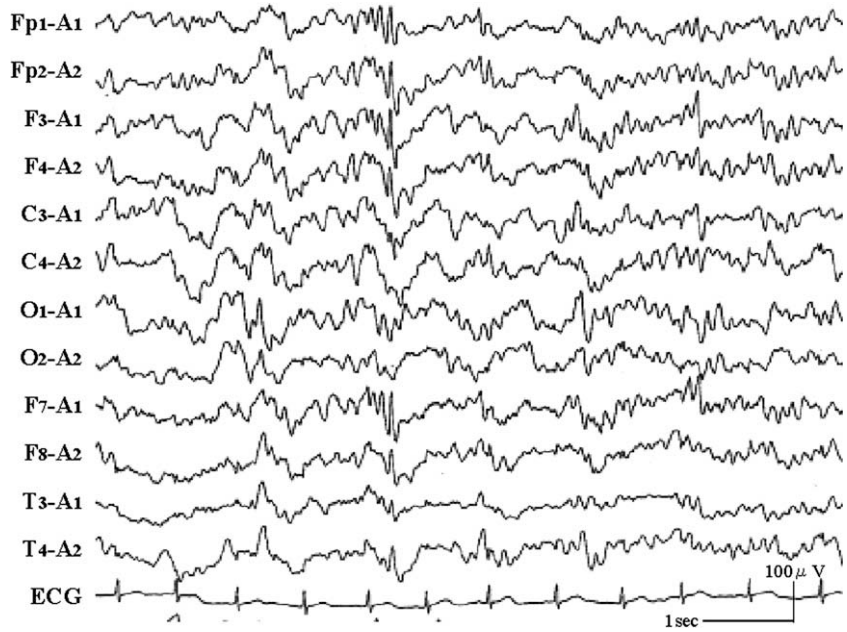

Fig. 1. Interictal electroencephalography showing transient sharp waves over the left frontal and temporo-frontal region with normal background activity.