Case Series
Volume 8:4, 2022

Epilepsy Journal

ISSN: 2472-0895 **Open Access**

Epileptic Encephalopathy: Case Series

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Abstract

Extreme cases of intractable childhood epilepsy might culminate in an illness called epileptic encephalopathy. Along with being fatal in certain instances, the illness can result in significant delays in the development of cognitive, sensory, and motor functions. Early infantile SCN8A encephalopathy is associated with missense mutations in SCN8A, which encodes Nav1.6, a key subunit of the voltage-gated sodium channel in neurons and muscles. In this case report, we describe a 5-month-old child who has a new missense mutation associated with SCN8A encephalopathy. The findings of blood and metabolic testing, electroencephalogram (EEG), and brain magnetic resonance imaging (MRI), with the exception of uncontrollable seizures and autistic characteristics, were all normal. Genetic sequencing should be taken into consideration to determine the underlying genetic origins of these mutations since the phenotypes brought on by these mutations cannot be distinguished by any clinical, neuroimaging, or electrophysiological criteria. The administration of oxcarbazepine, as opposed to phenytoin, which is advised as a last-resort treatment for SCN8A encephalopathy, reduced this patient's uncontrollable seizures.

Keywords: SCN8A • SCN8A encephalopathy • Oxcarbazepine

Introduction

Epileptic encephalopathy (EE) is a term used to describe circumstances in which persistent epileptic activity is the primary cause of severe developmental delays, such as impairments in cognitive and behavioural development [1]. Due to the discovery of novel genetic variations that cause a number of severe early onset epilepsies, changes in public awareness, and the more early detection of the accompanying developmental delays, the clinical understanding of EE has recently undergone significant change. As a result, a new name, "developmental epileptic encephalopathy" (DEE), has been developed for people who have intellectual disabilities or developmental delays as a result of co-existing non-progressive brain conditions. It should be noted, however, that epilepsy itself may occasionally directly cause epileptic encephalopathy, whereas in other instances, the onset of the observed developmental delays may take place before or be completely unrelated to any epileptic seizures or abnormalities of the epileptic form [2,3]. Accordingly, DEE refers to a variety of severe illnesses with a variety of etiologies [4,5], and in certain instances, these different etiologies may result in a delayed or missed diagnosis.

The voltage-gated sodium channel subunits Nav1.1-1.9 are encoded by nine genes that have been found and functionally described [6]. The Nav1.6 subunit, which is produced by the SCN8A gene and forms a complex with subunits to allow Na^+ to traverse cell membranes, maintain electrochemical gradients, and cause action potentials in neurons and muscles, is encoded by the SCN8A gene [7]. The four S4 transmembrane segments in SCN8A, which consists of four transmembrane domains with each having six segments (S1-S6), are in charge of the voltage sensor [7]. The SCN8A gene has been related to DEE through missense mutations, and pathogenic variations of the gene have been associated with a variety of symptoms in patients, including early onset and persistent seizures, intellectual incapacity, motor abnormalities, and a high mortality [7]. Phenytoin appears to be more effective at inhibiting the mutant channel. In this study, we describe the case of a 5-month-old girl who has SCN8A encephalopathy due to a new SCN8A mutation. Her uncontrollable seizures stopped after being given the anticonvulsant oxcarbazepine rather than phenytoin. To the best of our knowledge, this case represents the first in Asia and the second case worldwide in which the patient's point mutation was identified.

Case Report

The patient, a girl newborn named G1P1, was delivered naturally at a gestational age of 40 3/7 weeks with a birth weight of 2900 g and Apgar scores of 8 and 9, respectively, at 1 and 5 min. There was no evidence of a seizure-prone family. Her height was 62 cm, and her body weight was 6.3 kg (15-50th percentile) (15-50th percentile). Her age-appropriate developmental milestones were met. The child had seizures for the first time at age 5 months. Her seizures went from 3 per day to over 40 per day over time, increasing in frequency. The upward gaze, drooling, neck extension, tonic limbs, and myoclonic seizures of the shoulders, which were followed with localised twitching over her left forearm or the absent phenotypic, were characteristics of the seizure pattern. Negative findings came from a variety of EEG, brain MRI, and biochemical tests, including a metabolic screening, neurotransmitter studies, and a cerebrospinal fluid work-up. Despite the administration of phenytoin (20 mg/kg loading dosage, at least three times on various days, and 5 mg/kg maintenance dose), levetiracetam (30 mg/kg/day), phenobarbiturate (5 mg/kg/day), and valproate (15 mg/kg/day), the seizures remained. Her tonic seizures were resolved with the addition of the oral anticonvulsant oxcarbazepine (4 mg/kg/day), and when the dose of the oral oxcarbazepine was increased to 20 mg/kg/day and she ceased taking other AEDs, her frequency of seizures was decreased to 0-1 per day. She additionally displayed an autistic phenotype in addition to seizures. Through whole-exome sequencing, a mutation in SCN8A (c.5594T>C; p.L1865P) was discovered and later verified to be a de novo mutation. The infant is presently receiving treatment for her developmental delays through a rehabilitation programme (which includes physical, occupational, and language rehabilitation). She also goes to a mental health facility for her autism.

Discussion

In recent years, a growing number of SCN8A-related phenotypes have been discovered as a result of the more widespread use of genetic screening for epileptic syndrome patients. One percent of DEEs contained pathogenic SCN8A variants. There have been reports of early seizure start, uncontrollable

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Date of Submission: 24 September, 2022; Manuscript No: elj-22-75873; **Editor assigned:** 27 September, 2022, PreQC No: P-75873; **Reviewed:** 07 October, 2022, QC No: Q-75873; **Revised:** 12 October, 2022, Manuscript No: R-75873; **Published:** 18 October, 2022, DOI: 10.37421/2472-0895.2022.8.170

seizures, intellectual incapacity, motor abnormalities, and a disproportionately high mortality rate in people with SCN8A DEEs. In addition, some patients with benign epileptic syndromes and average IQs have also been shown to have SCN8A mutations. There have also been reports of patients with ID or movement disorders without epilepsy. Given these variances, it is difficult to obtain an early diagnosis and administer the appropriate treatments for patients with SCN8A DEEs. These variations include wide variability in symptoms and variable therapeutic responses among individuals sharing one and the same gene mutation. In a related effort, we searched the PubMed, Google Scholar, and Embase databases using the term "SCN8A" and included all relevant papers that met the following criteria: (1) clinical human studies, (2) reports regarding SCN8A variants and/or protein changes, and (3) case reports or original studies. Our goal was to gain a more thorough understanding of the clinical presentations of SCN8A DEEs and to better predict the altered functions of this mutated point. Finally, nine papers that fit these requirements were chosen. For comparison with the patient described in the present research, a total of 26 individuals with mutant SCN8A were included in these papers.

Variable psychomotor delays after seizure onset, normal brain MRI findings, focal and/or generalised seizures (tonic, myoclonic, absence), epileptic spasms with a normal EEG background activity, and rare febrile seizures are just a few of the unusual clinical presentations that can result from a mutation in the SCN8A gene. Therefore, targeted sequencing should be used to identify the underlying genetic causes in cases of epileptic encephalopathy in which the patient exhibits normal blood and biochemical investigation results, normal brain MRI and EEG results, and no reduction in seizures after pyridoxine or pyridoxal-5-phosphate treatment. Further supporting the use of gene sequencing to pinpoint the precise mutations underlying cases of epileptic encephalopathy are these notable functional variations in the impact of SCN8A mutations. A focused neuroprotective treatment strategy may be developed with the help of such an approach, which might significantly improve the long-term health outcomes for people with epileptic encephalopathy. It may also help clinicians choose the best medications and inform prognosis advice. It's significant that the patient in this example responded well to the drug oxcarbazepine.

Conclusion

The best way to find the signs of DEE with SCN8A mutation is to do a complete physical examination, detailed history collection, lab tests, brain imaging, and, most importantly, have a high level of suspicion. The case described in the present report has drawn our attention to the fact that targeted sequencing may be helpful in identifying the underlying genetic causes in patients with epileptic encephalopathy who have normal blood and biochemical investigation results, normal brain MRI and EEG results, and no reduction in seizures after pyridoxine or pyridoxal-5-phosphate treatment. Despite the fact that SCBs like phenytoin are advised as a last-resort treatment for SCN8A encephalopathy, the administration of oxcarbazepine may be taken into consideration in patients with mutant SCN8A who have uncontrollable seizures, at least in this situation.

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How to cite this article: Chuen, Hueng. “Epileptic Encephalopathy: Case Series.” Epilepsy J 8 (2022): 170.