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A Case Report on SCN2A-Related Developmental and Epileptic Encephalopathy and Benign Familial Infantile Seizures

Muhammed Nishad P[1], A. Priya[2], K. Arun Chander[3]

[1]Clinical Pharmacist, Department of Clinical Pharmacology, Apollo Children's Hospital, Chennai, Tamil Nadu, India
[2]Executive, Department of Clinical Pharmacology, Apollo Children's Hospital, Chennai, Tamil Nadu, India
[3]Consultant and Head, Department of Clinical Pharmacology, Apollo Children's Hospital, Chennai, Tamil Nadu, India

Corresponding Author: Dr. K. Arun Chander

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ABSTRACT

The phenotypic spectrum of SCN2A-related epilepsy was broad, ranging from benign epilepsy in neonate and infancy to severe epileptic encephalopathy. Developmental and epileptic encephalopathy and benign familial infantile seizures are caused by heterozygous mutations in the SCN2A gene.
Developmental and epileptic encephalopathy is a neurologic disorder characterized by the onset of seizures in the first days, weeks, or months of life. Seizures comprise multiple types, including tonic, generalized, and myoclonic, and tend to be refractory to medication. Additional common features include microcephaly, hypotonia, and abnormal movements, such as dystonia, dyskinesias, and chore athetotic movements. The phenotype is highly variable, even in patients with the same mutation.
Benign familial infantile seizure is a seizure disorder of early childhood with age at onset from 3 months up to 24 months. It is characterized by brief seizures beginning with a slow deviation of the head and eyes to one side and progressing to generalized motor arrest and hypotonia, apnoea and cyanosis, and limb jerks.
Seizures that begin shortly after birth or in infancy and are not associated with fever may suggest an SCN2A-related disorder. Genetic testing is required to confirm a diagnosis. Treatment for SCN2A-related disorders will depend on the type and severity of the seizures. Even Sodium channel-blocking medications are more effective, a combination of seizure medications is typically used to control the different seizure types.

KEYWORD: SCN2A gene, Developmental and epileptic encephalopathy, Benign familial infantile seizures, Genetic testing.

INTRODUCTION

Sodium channel protein type 2 subunit alpha, is a protein present in humans that is encoded by the SCN2A gene. Pathologic variants ("mutations") in the SCN2A gene cause a range of neurological conditions, including Developmental and epileptic encephalopathy and benign familial infantile seizures[1].

In children with SCN2A-related developmental and epileptic encephalopathy, the pathogenic variant may affect the SCN2A sodium channel in different ways[2]. In some cases, the SCN2A mutation leads to overactivity of the ion channel; in other cases, the mutation leads to decreased activity of the ion channel. Changes in the flow of sodium ions in the

brain cause epilepsy and associated developmental differences.

SCN2A-DEE is characterized by developmental delay or regression, intellectual disability, and frequent seizures that are often difficult to control with medication[2]. The seizures may be focal or generalized, and they can occur multiple times a day or even continuously. Other symptoms may include movement disorders, sleep disturbances, and behavioral problems.

The diagnosis of SCN2A-DEE is typically made based on the presence of characteristic symptoms, as well as results from genetic testing[8,9]. A thorough physical and neurological exam, along with imaging studies such as an electroencephalogram (EEG) and magnetic resonance imaging (MRI), may be performed to rule out other underlying causes of seizures and developmental delays[3]. Genetic testing is an important tool in the diagnosis of SCN2A-DEE, and it can identify mutations in the SCN2A gene that are known to be associated with the disorder[8,9].

There is no cure for SCN2A-DEE, but treatment usually involves antiepileptic medications to control seizures[6]. In some cases, other medications may be prescribed to manage other symptoms such as movement disorders and sleep disturbances. Early intervention and therapy can help with developmental delays and intellectual disability.

Benign familial neonatal/infantile seizures are a rare form of SCN2A-related disorders that is less severe than SCN2A-developmental and epileptic encephalopathy[2,4]. This type of disorder is characterized by seizures that begin during infancy or early childhood[10].

BFIS is typically characterized by brief seizures that usually last for a few seconds up to a minute. The seizures are usually generalized and involve both sides of the brain, resulting in stiffening or jerking of the arms, legs, or body.

BFIS is usually diagnosed based on the presence of characteristic symptoms, family history, and genetic testing[5]. There is no cure for BFIS, but the seizures can usually be controlled with antiepileptic medications such as carbamazepine, valproic acid, or levetiracetam[7]. In some cases, medications may not be necessary, and seizures may resolve on their own as the child grows older.

CASE REPORT

An 8 months old female baby was admitted for generalized tonic-clonic seizure on 12th November 2022 with antenatal history of the mother had covid positive at 29 weeks of gestation, was admitted to ICU and needed steroid/tocilizumab/O2 support and recovered well, delivery in term and no neonatal history. The baby was developmentally normal till 6 months, head holding at 3 ½ - 4 months, eye contact at 3 ½ months, eye contact was till 6 months, turns to sounds, and was able to sit on support. Baby had started seizures initially in the form of myoclonic jerks at 7 months of age, involving blinking of eyes, and hands which are primarily diagnosed as infantile spasms/tonic seizure/tonic-clonic seizure.

On general examination, she was drowsy, hypotonic, central – no head holding, peripheral – no eye contact, and regression of milestones. Had one episode of myoclonic seizure involving left upper limb and lower limb in a brief period of fewer than 30 seconds, subsided spontaneously, oral levipil maintenance dose given. For further management, the baby was shifted to PICU. On arrival to PICU, the baby was sleepy, hypotonic (lower limb and upper limb), pupils reactive, pulses normal, CBG – 107mg/dl, HR – 99-120 beats per minute, RR – 40-50 breaths per minute, SPO2: >97%. Baseline investigations were completed and found to be within normal limits. MRI brain done with MRA reported a normal study of the brain parenchyma and MR spectroscopy. CSF glycine level was within normal limits. EEG showed bilateral epileptiform discharges with hypsarrhythmia. She was treated with

Antiepileptics (Syp. Levetiracetam 50mg/kg/day, Tab. Vigabatrin 30mg/kg/day, Tab. Clonazepam 0.01mg/kg at night) and Prednisolone 2mg/kg/day. There were no further episodes of GTCS, she is clearly stable, hence being shifted to the ward on 15th November 2022.

In the ward, she had recurrent episodes of seizures. In view of the loss of function mutation, Syp. Sodium valproate (30mg/kg/day) was added. Syp. Melatonin (0.1mg/kg at night) was added as an adjunctive drug to decrease epileptic seizure frequency. Since the baby presented with clinical indications of global developmental delay, regression, seizures, and hypsarrhythmia, a blood sample was collected on 16th November 2022 and sent for performing Genetic Whole Exome Sequencing.

On 7th December 2022, a Genetic Whole Exome Sequencing report came which revealed that a heterozygous missense variation in exon 15 of the SCN2A gene that results in the amino acid substitution of Glutamine for Arginine at codon 853 was detected suggestive of Developmental and Epileptic Encephalopathy-11 (DEE11) (OMIM#613721); Benign Familial Infantile Seizures-3 (BFIS3)(OMIM#607745). In view of this pathology, Syp. Lacosamide (2mg/kg/day) was added. The child received stimulation practices for the acquisition of milestones. Parental counseling was done regularly about the condition of the ongoing treatment regimens. Genetic counseling was also done for the parents to understand the risk of passing on the condition to their children. Advised to continue antiepileptic drugs along with prednisolone and instructed to continue by tapering the dose after discharge. The child was improved clinically better and hemodynamically stable. Hence, she was discharged with advice on 23rd December 2022.

DISCUSSIONS

SCN2A-related developmental and epileptic encephalopathy (DEE) is a genetic disorder caused by mutations in the SCN2A gene, which provides instructions for making a protein that is essential for the proper functioning of neurons in the brain[1,2]. It is characterized by seizures, developmental delays, and intellectual disability, which often manifest in the first year of life[2]. Missense mutations are the most common type of SCN2A mutation and it results in a partial loss of function of the SCN2A protein, leading to abnormal neuronal activity in the brain.

Genetic testing is an important diagnostic tool for SCN2A-related DEE[8,9]. Whole exome sequencing (WES) is a particularly useful tool as it can analyze all the genes in a person's genome, including SCN2A, to identify potential disease-causing mutations[5,8]. Other diagnostic tests, such as brain imaging and electroencephalography (EEG), may also be performed to assess the severity and type of seizures and any structural abnormalities in the brain[3]. Any abnormalities in the EEG or Brain imaging support the diagnosis of this disorder.

Treatment options mainly focus on managing the symptoms and improving the quality of life for affected individuals. Antiepileptic drugs (AEDs), such as sodium channel blockers or benzodiazepines are highly recommended as initial treatment has a better effect on reducing the recurrent episodes of seizures[6,7]. The use of Melatonin along with antiepileptic drugs is very effective in reducing the frequency of seizure episodes.

Benign familial infantile seizures (BFIS) is a rare genetic disorder that affects infants and young children[2,10]. It is characterized by recurrent seizures that typically begin between 3 and 12 months of age and resolve by 18 to 24 months of age[2,4]. The hallmark symptom of BFIS is recurrent seizures, which are typically focal in nature, meaning they originate in a specific part of the brain. The seizures may involve jerking movements of the limbs or face, staring episodes, or brief periods of unconsciousness.

Clinical presentations and genetic testing are typically used to evaluate benign

familial infantile seizures (BFIS)[5]. Performing an electroencephalogram (EEG) to evaluate brain activity and identify abnormal electrical patterns associated with seizures can help to confirm the diagnosis[3]. Antiepileptic drugs (AEDs) such as valproic acid and carbamazepine are commonly used to control seizures in patients with BFIS[7]. Genetic counseling is recommended for the parents to understand the risk of passing on the condition to their children.

It is important to identify an early provisional diagnosis and to initiate the treatment immediately. Early diagnosis allows for early intervention and management of symptoms. Early intervention can help improve developmental outcomes, reduce the frequency and severity of seizures, and improve the overall quality of life.

CONCLUSION

SCN2A-related developmental and epileptic encephalopathy is a rare genetic disorder characterized by developmental delays or regression, intellectual disability, and frequent seizures that are often difficult to control with medication. Diagnosis is typically made based on symptoms and genetic testing, and treatment involves medications to control seizures and other interventions as needed to manage other symptoms.

BFIS is a rare genetic disorder that causes recurrent seizures during infancy or early childhood. Diagnosis is typically based on symptoms, family history, and genetic testing, and treatment involves antiepileptic medications to control seizures. An early provisional diagnosis of SCN2A-related epileptic disorders is essential for early intervention, genetic counseling, and improving our understanding of the disorder. In this case, the treatment strategies were used as well and the patient too responded well.

Declaration by Authors

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