Case Report

A Novel Case of *SCN1A* Mutation Presenting as Hyperkinetic Movement Disorder

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Abstract

SCN1A mutation is most often associated with Dravet syndrome, which is characterized by severe encephalopathy. One of the other presentations of *SCN1A* mutation is developmental and epileptic encephalopathy-6B (DEE6B). It is a severe neurodevelopmental disorder characterized by early-infantile seizure onset, profoundly impaired intellectual development, and a hyperkinetic movement disorder. Here we report a rare case of novel *SCN1A* mutation presenting as hyperkinetic movement disorder in the form of multifocal dystonia and parakinesia in a 12-year-old boy, which aggravated with the use of sodium channel blockers.

Keywords: Cannabinoids, cerebellar atrophy, Dravet syndrome, dystonia, *SCN1A* mutation

Introduction

SCN1A encodes the alpha subunit of neuronal voltage-gated sodium channel.[1] Mutations in the *SCN1A* gene cause Dravet syndrome in about 80% of cases.[2] One of the other presentations of *SCN1A* mutation is developmental and epileptic encephalopathy-6B (DEE6B). It is a severe neurodevelopmental disorder characterized by early-infantile seizure onset, profoundly impaired intellectual development, and a hyperkinetic movement disorder.[3] However, *SCN1A* mutation manifesting as hyperkinetic movement disorder without seizures has not been reported so far. This is a case of novel *SCN1A* mutation presenting as hyperkinetic movement disorder in the form of multifocal dystonia and parakinesia.

Case Report

A 12-year-old boy, the first born child of a nonconsanguineous marriage, with an uneventful birth history presented with developmental delay in motor and language milestones. He had swaying since he started walking, which was slowly progressive in nature. He was ambulant and went to school till 11 years of age. At the age of 11, he had one episode of right focal seizure with secondary generalization and was given carbamazepine. Since he had subsequent episodes of seizures, levetiracetam was added. Over the next few weeks, he developed abnormal posturing of the left upper limb that increased during action, stress and was relieved during sleep, which was followed by posturing in other limbs, frequent rubbing of both eyes with increased blinking, and difficulty in opening the mouth. All these symptoms had diurnal variation, which presented as increased episodes and duration in the evening and were progressive over the day.

On examination, he was conscious and oriented. He had blepharospasm, oromandibular and laryngeal dystonia, cervical dystonia, left focal limb dystonia, and lingual chorea with parakinesia. Cranial nerves were intact and there was no weakness of limbs. Sensations were intact. He had stance ataxia and gait ataxia. There was no nystagmus or appendicular ataxia. Fundi were normal. Other systemic examination was normal.

On investigation, complete blood count, liver and renal parameters, blood sugar, lipid profile, thyroid profile, peripheral smear for acanthocytosis, serum ceruloplasmin, uric acid, parathyroid hormone, anti-streptolysin O titer, and tandem mass spectrometry were normal.

No Kayser-Fleischer (KF) ring was noted in slit-lamp examination. Magnetic resonance imaging of the brain showed diffuse cerebellar atrophy; basal ganglia were normal [Figure 1a and b]. Electroencephalogram showed diffuse background slowing.

Anticholinergics and baclofen were given for dystonia. The Dopamine (DOPA) trial was not successful. Despite the control of seizures, carbamazepine was continued due to the suspicion of paroxysmal kinesogenic dyskinesia for which carbamazepine is the drug of choice. Anti-dystonia drugs were escalated and benzodiazepines were added. Serum alpha-fetoprotein and immunoglobulin profile were

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Submitted: 11-Dec-2023 **Revised:** 06-Mar-2024 **Accepted:** 09-Mar-2024
Published: 12-Apr-2024

DOI: 10.4103/aian.aian_1080_23

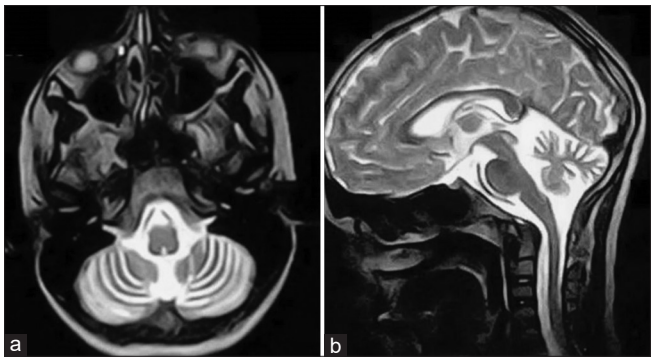

Figure 1: (a) Axial T2 image showing diffuse cerebellar atrophy. (b). Midline sagittal T2 image showing diffuse cerebellar atrophy

normal. Dystonia was progressive despite the patient being on medications.

Genetic analysis was planned and whole exome sequencing revealed heterozygous missense variation in exon 28 of the *SCN1A* gene (chr2:g. 165994286G>A; depth: 179×), which results in amino acid substitution of isoleucine for threonine at codon 1571 (p.Thr1571Ile; ENST00000674923.1), suggestive of DEE6B, a non-Dravet variant of *SCN1A* mutation. As per the American College of Medical Genetics & Genomics (ACMG) criteria, the reported mutation falls under likely pathogenic variant. Carbamazepine was stopped immediately. Following this, dystonia partially improved with drug titrations. During follow-up, worsening of bulbar dystonia was noted in the form of dysphagia. Drug dosage was titrated, and the patient was advised regular follow-up.

Discussion

SCN1A gene encodes the alpha 1 subunit of the sodium channel and has been associated with several epileptic and nonepileptic syndromes. *SCN1A* depicts the archetypal channelopathy associated with a wide phenotypic spectrum of epilepsies that range from genetic epilepsy with febrile seizures plus to developmental and epileptic encephalopathies (DEEs).[4] The main aim of treating an epileptic encephalopathy is to suppress epileptiform activity and thereby facilitate developmental progress. By optimally managing specific epileptic encephalopathy, a good long-term outcome is expected.[3] Nowadays, an increase in recognition regarding the overlap of DEEs and movement disorders has been observed. Several severe hyperkinetic (dystonia, choreoathetosis, myoclonus) movements have been described in a range of genetic encephalopathies caused by *SCN2A*, *SCN8A*, *FOXG1*, *STXBP1*, *GNAO1*, *ARX*, and *DNM1*.[5,6] However, in all these cases, encephalopathy as a predominant feature with refractory seizures and movement disorders was a part of the presentation.[7-9] In this case, hyperkinetic movement disorder was predominant with discrete episodes of seizures.

The presentation of hyperkinetic movement disorder and dyskinesia with discrete episodes of seizure got aggravated with the use of carbamazepine. This unique presentation compelled us to proceed further with a genetic evaluation, which eventually revealed the presence of a loss-of-function mutation of the *SCN1A* gene. Following this, the sodium channel blocker was stopped, which led to clinical improvement. This kind of hyperkinetic movement disorder with dyskinesia in *SCN1A* mutation has not been reported previously in the literature. This genotypic and phenotypic correlation led to adopt an individualized approach to manage this patient. Such an individualized approach would aid in better clinical outcomes.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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