Case report

A Novel *SCN8A* mutation in a case of early-onset infantile epileptic encephalopathy: A Case Report

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Abstract. SCN8A gene encodes sodium channel alpha subunit $Na_v1.6$, and its mutation is associated with Early Infantile Epileptic Encephalopathy-13 (EIEE-13). The mean age of onset is 4-5 months. The phenotype of SCN8A mutation varies from benign epilepsy syndromes, movement disorder, intellectual disability to severe epileptic syndromes with different types of seizures. We hereby report a case of a one-year old female who had an onset of infantile spasms on the seventeenth day of life, which gradually progressed to focal, multifocal, GTCS, and epileptic encephalopathy by one year of age associated with global developmental delay and hypotonia. All metabolic workup, TMS, GCMS, and MRI brain were normal. EEG at 2.5 months was suggestive of epileptic discharge arising from the left frontal region, evolving into generalized discharges. Whole exome sequencing revealed a heterozygous mutation in the SCN8A gene at exon 16 (p.Val892Ala) suggestive of Early Infantile Epileptic Encephalopathy-13 (EIEE-13). This is a novel mutation in the SCN8A gene which has not been reported previously in the literature. (www.actabiomedica.it)

Key words: *SCN8A* encephalopathy, Early Infantile Epileptic Encephalopathy-13 (EIEE-13)

Background

Early infantile epileptic encephalopathy is a severe form of intractable seizures in the first year of life, resulting in severe neurodevelopmental impairment (1). To date, more than 70 genes are known to cause epilepsy and neurodevelopment disorders - *SCN1A* and *KCNQ2* being the commonest (2). *SCN8A* gene mutation, which encodes sodium channel alpha subunit $Na_v1.6$, was first reported in 2012, and since then, there are more than 50 published cases (3–5). *SCN8A* mutation attributes 1-3.6% of the total cases of infantile-onset epileptic encephalopathy and is now classified as *SCN8A* encephalopathy or Early Infantile Epileptic Encephalopathy-13 (EIEE-13) (2,4–6).

SCN8A gene is located in chromosome 12q13.13. It contains 26 coding exons and two pairs of alternatively spliced exons, measures 170 kb, and is composed of 1980 residues (7). The voltage-gated sodium channel, $Na_v1.6$, is highly concentrated in the axon initial segment and nodes of Ranvier of the neurons in the central nervous system. The protein structure comprises four homologous domains, DI-DIV, each domain comprising six transmembrane segments, S1-S6 (Figure 1). There are two large interdomain cytoplasmic loops between DI-DII and DII-DIII. There is a short loop between DIII-DIV, which is highly conserved and serves as an inactivation gate of the $Na_v1.6$ channel. Unlike the other sodium channels ($Na_v1.1$, $Na_v1.2$), $Na_v1.6$ has a lower threshold and can sustain repetitive excitation and firing. Hence, the mutation in this channel can lead to seizures (7). Of the 50 published cases, 31 pathogenic mutations have been described, most of them

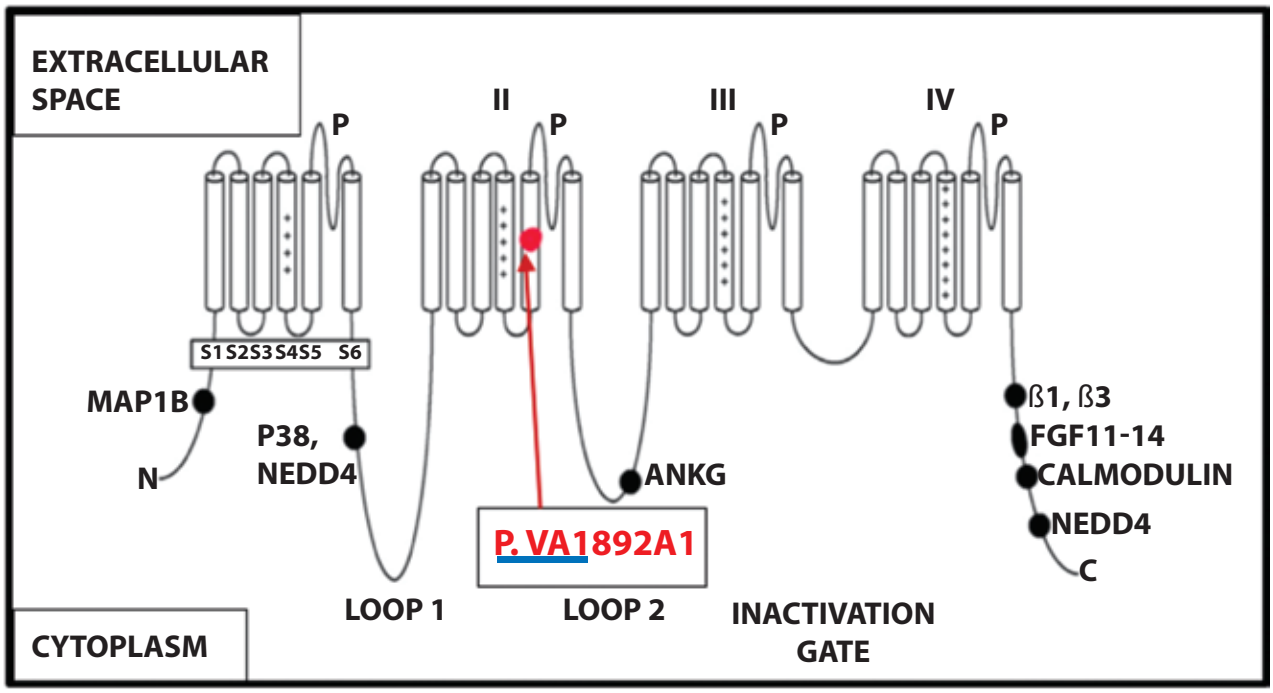

Figure 1. Location of mutation in *SCN8A* gene- *SCN8A* gene encodes for Nav1.6 channel (7). Nav1.6 consists of four homologous domains (DI- DIV), each having six transmembrane segments (S1-S6), three cytoplasmic interdomains loops, N-terminal and C-terminal domains. The third small loop is highly conserved and functions as an inactivation gate. The large interdomain cytoplasmic loops 1 and 2 are less well conserved. p- pore loops. The mutation in our patient was at amino acid number 892, which is located in the S5 transmembrane segment of domain II.

being located in the transmembrane segments, N-, and C- domains (4). Residue number 1872 of the *SCN8A* gene is recognized to be a hotspot of mutation, where arginine is replaced by another amino acid. Other mutations that have been repeatedly described in patients are p.Thr767Ile, p.Arg1617Gln, p.Glu1483Lys, and many denovo mutations (4,8). The phenotype of *SCN8A* mutation varies from benign epilepsy syndromes to movement disorder to intellectual disability to severe epileptic syndromes with different types of seizures with poor genotypic-phenotypic correlation (3,4,6,8,9). We present a case of a denovo mutation in the *SCN8A* gene at exon 16 (p.Val892Ala) with neonatal onset and multiple types of seizures.

Case

A one-year-old female child, second in birth order of a non-consanguineous marriage with uneventful perinatal history, nutritionally normal and insignificant family history presented with seizures in the form of infantile spasms with onset at seventeenth day of life. The baby was conceived spontaneously to a 25-year-old woman with no prior illness with a history of one previous medically terminated pregnancy at three months of conception due to social issues. The baby was born as term, 38 weeks of gestation, by caesarian section in view of low-lying placenta with a birth weight of 2.9 kg and no history of perinatal asphyxia, feeding difficulties, seizures in the perinatal period, or neonatal hyperbilirubinemia. At day 17 of life, baby had history of infantile spasms in the form of sudden jerky movement of both upper limbs, four to five episodes in a day which was more prominent during sleep. It was construed as normal movements during sleep, not requiring any treatment. Exclusive breastfeeding practices were followed. However, at 1.5 months of age, the child was hospitalized for recurrent afebrile focal seizures in the form of twitching of the corner

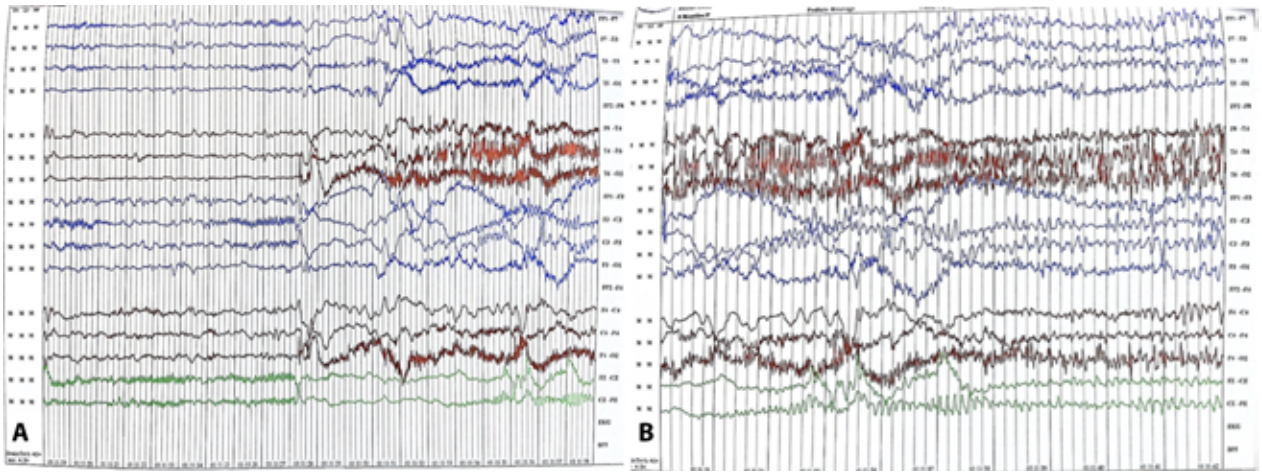

Figure 2. A, B): EEG of patient – EEG showing epileptic discharge arising from the left frontal region evolving into generalized discharges.

of the mouth, which progressed to multifocal seizures involving all four limbs and uprolling of eyeballs, associated with lethargy and decreased oral acceptance. Central nervous system examination was normal. Blood sugar, electrolytes, and sepsis screen were normal. CSF studies and ultrasound cranium ruled out meningitis. Seizure control was achieved with phenytoin, phenobarbitone, and levetiracetam.

The patient had repeated episodes of focal seizures of the upper limb every 10-15 days. At 2.5 months of age, the child presented with three episodes of seizures- GTCS and multifocal. By this age, the patient had not attained social smile or recognizing mother. However, tone, reflexes, fundus examination, hearing, and head circumference were normal without any feature suggestive of an inborn error of metabolism. Complete metabolic panel- blood sugar, calcium, magnesium, vitamin D, renal function tests, liver function tests, lactate, ammonia, urine for reducing substances, TMS (tandem mass spectrometry) on dried blood sample, and urine GCMS (gas chromatography-mass spectrometry) were normal. MRI brain was normal, but EEG was suggestive of epileptic discharge arising from the left frontal region evolving into generalized discharges (Figure 2).

With the progress of age to five months, the child developed multiple types of unprovoked seizures- focal, clonic, tonic, myoclonic, and generalized tonic-clonic with increasing frequency (5-6 times/day) with global developmental delay with axial and appendicular hypotonia and normal head circumference. Suspecting early-onset epileptic encephalopathy syndromes, a whole exome sequencing was done, which revealed a heterozygous mutation in the *SCN8A* gene at exon 16 (p.Val892Ala) suggestive of Early Infantile Epileptic Encephalopathy-13 (EIEE-13). Currently, the child is one year old with seizures controlled on multiple anti-epileptics, has axial and appendicular hypotonia, not achieved any milestone in any of the developmental domains (not recognizing mother, no social smile, complete head lag), with visual impairment but startles on sound. The seizure gets precipitated by acute illness.

Discussion

SCN8A encephalopathy, also known as EIEE-13, presents with intractable seizures at a mean age of onset of 4.5 months (4,8). Denis et al. have proposed that *SCN8A* patients have two modes of onset – type 1 having an early age of onset (median age-one month) and progresses over six to ten months with subtle seizures and usually normal interictal EEG; and type 2 being late-onset (median age- five months) with sudden and frequent seizures and rapid deterioration within a month to epileptic encephalopathy and abnormal

interictal EEG (6). Type 1 is further divided into type 1a and 1b depending on the presence or absence of seizure. Out of the nineteen patients in their study, six, six, and seven patients were of type 1a,1b, and 2, respectively (6). Our patient fits into type 1a as the age of onset of seizures was seventeen days, and it progressed to epileptic encephalopathy over one year.

The patient had all types of seizures except absence seizures. A systematic review article of 50 published cases has mentioned the incidence of GTCS, absence, focal, clonic, and epileptic spasms to be 42%, 20%, 20%, 12%, and 12%, respectively (4). The patient had hypotonia in consistence with 44-48% of the reported cases (4,6,8,9). There are few reported cases of hypertonia as well (3,10,11). The child did not present with any movement disorder like ataxia, dystonia, hyperreflexia, or choreoathetosis, reported in 26%, 12%, 8%, 8% cases, respectively (3,4,10). The child had an overall developmental delay on all fronts. Denis et al. have reported normal development before the onset of seizures in 83% in type 1a and type 1b each, and 73.6% overall with regression in 47.3% after the onset of seizures (6). In the systematic review of 50 patients, 58% presented with developmental delay, and 20% presented with regression (4).

Previous studies have documented moderate to severe intellectual disability in 76% to 95% cases (4,6,8). However, there has been a case report of an autosomal dominant variant of *SCN8A* mutation with very mild phenotype with early-onset epileptic seizures without neurological or cognitive impairment (12). Autistic features have also been reported (13,14). Our patient had visual impairment in the form of not showing interest in the objects shown. Visual impairment is present in 41% cases (8). The head circumference was normal, which is also a common presentation (58%) (6).

The child had normal MRI brain as present in 50-60%, but other MRI features like diffuse cortical atrophy, cortical atrophy in frontal and pre-frontal region, hypoplasia of corpus callosum, and white matter hyperintensities may be present (6,8). EEG may be normal in nearly 50%, with the most common abnormality being focal/ multifocal epilepsy as described in this case, and others being hypsarrhythmia, slowing of background with burst-suppression pattern, and generalized spike and wave (6,8,10,11). EEG pattern evolves over time (3,14).

Most patients have refractory seizures requiring multiple anti-epileptics and sodium channel blockers like phenytoin, carbamazepine, and lamotrigine to control seizures (6,8,9). However, there have been three instances of seizures being aggravated by lamotrigine and carbamazepine (6). The patient responded to high dose phenytoin (8 mg/kg/day), levetiracetam (40 mg/kg/day), phenobarbitone (5mg/kg/day) and clonazepam (0.02 mg/kg/day). There is a 10-20% risk of sudden unexpected death in epilepsy (SUDEP) (4,6,8).

The whole-exome sequencing diagnosed a heterozygous mutation in the *SCN8A* gene at exon 16 (p.Val892Ala), which is a pathological variant. The location of this amino acid is in the S5 of the transmembrane segment of domain II (DII) (Figure 1) as gathered on uniport.org (https://www.uniprot.org/uniprot/Q9UQD0) (15).

Pathogenic mutations are mostly concentrated in N- and C- terminal domains and transmembrane segments (4). Ours is a novel mutation that has not been reported previously. Larsen et al. have reported mutation at the 890th amino acid (Ala890Thr), which is closest to the mutation at 892nd amino acid (8). The patient's phenotype is mild, presenting with developmental delay, the onset of seizures at nine months in the form of nocturnal bilateral convulsive seizures and cyanosis, moderate hypotonia with patient speaking in single words, and having ADHD features at four years of age (8).

A correlation between the severity of phenotype and location of mutation has not been found (6,8). Even mutations in the same gene have resulted in varied presentations (4,6,8). This highlights that the phenotypical spectrum associated with variations in each gene can vary widely. The spectrum of clinical manifestations can have a wide range of phenotypic severity from self-limited neonatal-onset epilepsies to early-onset epileptic encephalopathies.

Conclusion

Our study further strengthens the association of *SCN8A* mutation associated with early-onset epileptic encephalopathy. The mutational analyses helped in

prognosticating the parents about the developmental delay, refractory seizures, risk of SUDEP, and genetic counseling in future pregnancies. Due to resource-limited settings and financial constraints, the parents could not get their *SCN8A* mutation analysis. *SCN8A* should be routinely evaluated in a case of infantile epileptic encephalopathy where other common causes are excluded.

Abbreviations: EIEE-13: Early Infantile Epileptic Encephalopathy-13; GCMS: gas chromatography-mass spectrometry; *SCN8A*: Sodium channel, voltage gated, type VIII, alpha subunit; SUDEP: sudden unexpected death in epilepsy; TMS: tandem mass spectrometry

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