EARLY-ONSET DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY ASSOCIATED WITH A DE NOVO SCN8A VARIANT (P.VAL410LEU): A CASE REPORT

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Abstract. *The SCN8A gene encodes the neuronal voltage-gated sodium channel NaV1.6, which plays a critical role in neuronal excitability. Pathogenic variants in SCN8A are associated with a broad clinical spectrum ranging from benign familial infantile seizures to developmental and epileptic encephalopathy (DEE13). Gain-of-function variants are frequently linked to early-onset epilepsy and severe neurodevelopmental impairment.*

Materials and methods*: Clinical assessment included neurological examination, sleep electroencephalography (EEG), brain magnetic resonance imaging (MRI), audiological evaluation, and whole-exome sequencing (WES). Variant interpretation followed ACMG/AMP guidelines. The identified variant was validated by Sanger sequencing. Case Presentation: We report a 15-month-old male presenting with early-onset epilepsy, profound developmental impairment, severe hypotonia, impaired visual fixation, and reduced auditory responsiveness. Sleep EEG demonstrated hypsarrhythmia. Brain MRI revealed corpus callosum hypoplasia and delayed myelination. Whole-exome sequencing identified a de novo pathogenic variant SCN8A:c.1228G>T (p.Val410Leu).*

Conclusion*: The clinical and electroencephalographic findings are consistent with SCN8A-related developmental and epileptic encephalopathy.*

Keywords: *SCN8A; developmental and epileptic encephalopathy; hypsarrhythmia; early-onset epilepsy; whole-exome sequencing.*

Introduction. Developmental and epileptic encephalopathies (DEEs) represent a group of severe neurological disorders characterized by early-onset seizures accompanied by developmental impairment [1]. Advances in genomic technologies have significantly improved the identification of monogenic etiologies underlying many DEEs [6].

The SCN8A gene encodes the α-subunit of the voltage-gated sodium channel NaV1.6, which is highly expressed at the axon initial segment and nodes of Ranvier [13, 15]. NaV1.6 plays a fundamental role in the initiation and propagation of action potentials [4].

Pathogenic variants in SCN8A are associated with a broad phenotypic spectrum. Mild phenotypes include benign familial infantile seizures [2, 12]. In contrast, severe presentations involve developmental and epileptic encephalopathy (DEE13), characterized by early seizure onset and profound developmental impairment [3. 11].

Functional studies demonstrate that many epilepsy-associated missense variants exert gain-of-function effects, resulting in neuronal hyperexcitability [4, 8]. Clinical severity has been shown to correlate with the functional consequences of the variant [9].

Electroencephalographic abnormalities in SCN8A-related DEE are heterogeneous, with reported findings including multifocal epileptiform discharges, generalized epileptiform activity, and hypsarrhythmia [10].

Here, we describe a clinical case of SCN8A-related developmental and epileptic encephalopathy with early-onset epilepsy and hypsarrhythmia confirmed by molecular genetic testing.

Materials and Methods.

Subject

The proband underwent clinical evaluation including neurological examination, prolonged video-EEG monitoring, brain magnetic resonance imaging (MRI), audiological assessment, and genetic testing. Clinical data were obtained through medical records review and caregiver interviews.

Electroencephalography

A 3-hour video-EEG monitoring study was performed during wakefulness and sleep using a digital EEG system. Electrodes were positioned according to the international 10–20 system. EEG recordings were analyzed for background activity, epileptiform discharges, and pathological patterns.

Neuroimaging

Brain MRI was performed using an epilepsy-specific protocol. Structural abnormalities, white matter maturation, and commissural structures were evaluated.

Genetic Analysis

Genomic DNA was extracted from peripheral blood samples obtained from the proband. Whole-exome sequencing (WES) was performed using next-generation sequencing technology. The SCN8A variant was supported by a read depth of 149×. Sequence reads were aligned to the human reference genome (GRCh38), followed by variant calling and annotation using a validated bioinformatics pipeline. Variant interpretation and classification were conducted according to ACMG/AMP guidelines [4].

Segregation and Parentage Analysis

The identified SCN8A variant was validated by Sanger sequencing in the proband and both parents. Segregation analysis confirmed a de novo occurrence. Biological parentage was verified.

Case Presentation

A 15-month-old male child was referred for neurological assessment because of recurrent seizures and profound developmental impairment. According to the caregivers, abnormal neurological features had been evident since the neonatal period. On the second day of life, the infant was described as lethargic with a weak sucking reflex. Despite early feeding difficulties, weight gain was considered adequate.

Beginning at approximately 2 months of age, the child developed episodes of prolonged inconsolable crying, predominantly occurring in the evening hours.

Seizures began between 5 and 6 months of age. The initial paroxysmal episodes were characterized by a sudden cry followed by frequent contractions involving both the upper and lower extremities. These events recurred multiple times per day over the course of approximately one month. At 7 months, the episodes were recognized as epileptic seizures, and valproate therapy (Convulex) was initiated. However, no clinical response was observed. Subsequent treatment with vigabatrin (Sabril) resulted in temporary seizure cessation.

At approximately 10 months of age, an afebrile episode paroxysmal episode characterized by impaired awareness and fixed gaze developed 2–3 days following vaccination. The episode lasted approximately 30 minutes. Hormonal therapy was introduced, with caregivers reporting a positive clinical effect. One month later, during a febrile respiratory illness, another seizure occurred and was described as tonic in nature, with open eyes, fixed gaze, and sustained limb hypertonia.

By 15 months of age, seizures recurred, predominantly upon awakening. These episodes were described as paroxysmal episode characterized by impaired awareness and fixed gaze associated with apparent respiratory discomfort, interpreted by caregivers as a sensation of “air hunger,” occurring two to three times daily. At the time of evaluation, the child remained on vigabatrin therapy; precise dosing information was unavailable.

The child was born at term (40 weeks of gestation) following an uncomplicated pregnancy to non-consanguineous parents. Delivery occurred via spontaneous vaginal birth. Birth weight was 3,500 g. The neonate cried immediately after birth. Family history was negative for epilepsy or hereditary neurological disorders. Two older siblings were healthy. One previous pregnancy ended in early miscarriage.

Importantly, developmental milestones were absent from birth. The child never acquired head control, visual fixation, or tracking abilities. Responsiveness to auditory stimuli, including the mother’s voice, was markedly reduced. Excessive sleep duration was reported.

Neurological examination revealed a child without visual fixation or tracking and with minimal auditory responsiveness. Severe axial hypotonia was observed, accompanied by a frog-leg posture and absence of head control. Deep tendon reflexes were present and symmetric. Pathological reflexes were not elicited. Sensory responses to tactile stimulation were reduced. No hyperkinetic movements were observed. Bulbar dysfunction was noted, including swallowing difficulties and choking episodes. A left-sided grade 1 conductive hearing loss was documented.

Sleep EEG demonstrated a markedly disorganized background pattern, dominated by medium- to high-amplitude slow activity in the theta and delta frequency ranges. Very frequent multifocal epileptiform discharges, including spikes and polyspikes, were recorded, accompanied by diffuse high-amplitude slow wave complexes. The EEG findings were interpreted as hypsarrhythmia.

Brain MRI performed using an epilepsy protocol revealed hypoplasia of the corpus callosum, delayed/incomplete myelination, a right temporal arachnoid cyst measuring 14 × 15 × 24 mm, and mega cisterna magna considered a developmental variant.

Whole-exome sequencing identified a heterozygous pathogenic variant in SCN8A (NM_001330260.2:c.1228G>T, p.Val410Leu). Trio Sanger sequencing confirmed the presence of the variant in the proband and its absence in both parents, consistent with a de novo event. Functional prediction suggested a gain-of-function effect.

Discussion.

SCN8A-related developmental and epileptic encephalopathy (DEE13) is increasingly recognized as a prototypical sodium channelopathy in which the functional direction of channel dysfunction (gain-of-function vs loss-of-function) is clinically meaningful for prognosis and treatment selection [5]. In most individuals with early-onset DEE, de novo missense variants predominate and frequently confer gain-of-function effects on NaV1.6, leading to neuronal hyperexcitability and severe developmental impairment [12]. Experimental data from heterologous systems and neuronal models support a genotype–phenotype continuum in which epilepsy-associated variants increase neuronal firing, whereas loss-of-function changes are more often linked to intellectual disability phenotypes without epilepsy [12].

The electroclinical presentation in SCN8A-DEE is heterogeneous but typically includes early seizure onset, multiple seizure types, and frequent pharmacoresistance [13]. Importantly, epileptic spasms and hypsarrhythmia have been documented within the SCN8A phenotypic spectrum, emphasizing that SCN8A should be considered among genetic etiologies of infantile spasms syndrome when electroencephalography demonstrates hypsarrhythmia [14]. In this context, the reported patient's early-onset epilepsy with profound developmental impairment and hypsarrhythmia aligns with severe SCN8A-DEE presentations described in the literature [13–14].

From a mechanistic standpoint, in vivo studies further implicate forebrain excitatory neurons as critical drivers of seizure burden and premature mortality in SCN8A encephalopathy models, reinforcing the concept that persistent network hyperexcitability underlies clinical severity in gain-of-function disease [15]. These observations support precision-medicine approaches aimed at reducing aberrant sodium current. Consistent with this, pharmacologic strategies that target persistent and resurgent sodium currents have shown preclinical efficacy in SCN8A gain-of-function models and provide a rationale for sodium channel–modulating therapies in selected patients [16]. However, treatment responses remain variable across variants and individuals, and careful alignment of therapy with suspected functional effect (including consideration of sodium channel blockers in gain-of-function disease) is recommended [11].

Recently, an international modified-Delphi consensus provided practical guidance for diagnosis and management of SCN8A-related epilepsy and neurodevelopmental disorders, highlighting the need for systematic phenotyping, variant-level interpretation, and individualized antiseizure medication selection [17]. Within such frameworks, confirming de novo status by segregation testing (and, when appropriate, parentage confirmation) strengthens causal attribution and supports accurate

recurrence-risk counseling, especially in severe early-onset presentations where clinical urgency is high [17].

Overall, the present case contributes to the accumulating evidence that SCN8A should be prioritized in infants with early-onset epilepsy and severe developmental impairment, particularly when spasms or hypsarrhythmia are present [14]. Integrating deep phenotyping with robust variant classification and segregation analysis remains central to establishing molecular diagnosis and informing rational, mechanism-oriented treatment strategies in SCN8A-DEE [11, 17].

Conclusion.

We describe a case of SCN8A-related developmental and epileptic encephalopathy caused by a de novo pathogenic variant SCN8A:c.1228G>T (p.Val410Leu), presenting with early-onset epilepsy, hypsarrhythmia, profound developmental impairment, and severe axial hypotonia.

This case reinforces the expanding electroclinical spectrum of SCN8A-associated disorders and supports the concept of genotype-driven disease stratification in sodium channelopathies. Early molecular diagnosis through comprehensive genomic testing is essential in infants with developmental and epileptic encephalopathy, as it enables accurate etiological classification, informs mechanism-based therapeutic considerations, and provides critical guidance for genetic counseling and long-term management.

REFERENCES

1. Bunton-Stasyshyn RKA, Wagnon JL, Wengert ER, et al. Prominent role of forebrain excitatory neurons in SCN8A encephalopathy. Brain. 2019;142(2):362–375. doi:10.1093/brain/awy324.

2. Catterall WA. Voltage-gated sodium channels at 60: structure, function and pathophysiology. J Physiol.2012; 590 (11):2577–2589. doi:10.1113/jphysiol.2011.224204.

3. Conecker G, Xia MY, Hecker J, et al. Global modified Delphi consensus on diagnosis, phenotypes, and treatment of SCN8A-related epilepsy and/or neurodevelopmental disorders. Epilepsia. 2024. doi:10.1111/epi.17992.

4. Gardella E, Marini C, Trivisano M, et al. The phenotype of SCN8A developmental and epileptic encephalopathy. Neurology. 2018;91(12):e1112–e1124. doi:10.1212/WNL.0000000000006199.

5. Larsen J, Carvill GL, Gardella E, et al. The phenotypic spectrum of SCN8A encephalopathy. Neurology. 2015; 84(5):480–489. doi:10.1212/WNL.0000000000001211.

6. Larsen J, Carvill GL, Gardella E, et al. The phenotypic spectrum of SCN8A encephalopathy. Neurology. 2015;84(5): 480–489. doi:10.1212/WNL.0000000000001211.

7. Liu Y, Schubert J, Sonnenberg L, et al. Neuronal mechanisms of mutations in SCN8A causing epilepsy or intellectual disability. Brain. 2019;142(2):376–390. doi:10.1093/brain/awy326.

8. Liu Y, Schubert J, Sonnenberg L, et al. Neuronal mechanisms of mutations in SCN8A causing epilepsy or intellectual disability. Brain. 2019;142(2):376–390. doi:10.1093/brain/awy326.

9. Meisler MH, Hill SF, Yu W. Sodium channelopathies in neurodevelopmental disorders. Nat Rev Neurosci. 2021;22(3):152–166. doi:10.1038/s41583-020-00414-9.

10. Oikawa S, et al. Treatment Options for Infantile Spasms Syndrome with SCN8A: A Case Report and Literature Review. 2024. doi:10.1055/s-0043-1778011.

11. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the ACMG and AMP. Genet Med. 2015;17(5):405–424. doi:10.1038/gim.2015.30.

12. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512–521. doi:10.1111/epi.13709.

13. Symonds JD, Zuberi SM, Stewart K, et al. Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort. Brain. 2019;142(8): 2303–2318. doi:10.1093/brain/awz195.

14. Talwar D, Hammer MF. SCN8A Epilepsy, Developmental Encephalopathy, and Related Disorders. Pediatr Neurol. 2021.

15. Wagnon JL, Meisler MH. Recurrent and non-recurrent SCN8A mutations: clinical and mechanistic implications. Brain.2015;138(Pt 7):1939–1952. doi:10.1093/brain/awv134.

16. Wengert ER, et al. Prax330 reduces persistent and resurgent sodium channel currents and protects against seizures in a model of SCN8A epileptic encephalopathy. 2019.

17. Zaman T, Helbig I, Boelman C, et al. SCN8A-associated developmental and epileptic encephalopathy: a multi-center cohort study. Brain. 2020;143(1):131–145. doi:10.1093/brain/awz337.