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Epileptic Disorders

CLINICAL COMMENTARY

Emergence of lingual dystonia and strabismus in early-onset *SCN8A* self-limiting familial infantile epilepsy

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Abstract

Pathogenic variants in *SCN8A* are associated with a broad phenotypic spectrum, including Self-Limiting Familial Infantile Epilepsy (SeLFIE), characterized by infancy-onset age-related seizures with normal development and cognition. Movement disorders, particularly paroxysmal kinesigenic dyskinesia typically arising after puberty, may represent another core symptom. We present the case of a 1-year-old girl with a familial disposition to self-limiting focal seizures from the maternal side and early-onset orofacial movement disorders associated with *SCN8A*-SeLFIE. Brain MRI was normal. Genetic testing revealed a maternally inherited *SCN8A* variant [c.4447G > A; p.(Glu1483Lys)]. After the introduction of valproic acid, she promptly achieved seizure control as well as complete remission of strabismus and a significant decrease in episodes of tongue deviation. Family history, genetic findings, and epilepsy phenotype are consistent with *SCN8A*-SeLFIE. Movement disorders are an important part of the *SCN8A* phenotypic spectrum, and this case highlights the novel early-onset orofacial movement disorders associated with this condition. The episodes of tongue deviation and protrusion suggest focal oromandibular (lingual) dystonia. Additionally, while infantile strabismus or esophoria is a common finding in healthy individuals, our case raises the possibility of an ictal origin of the strabismus. This study underscores the importance of recognizing and addressing movement disorders in *SCN8A*-SeLFIE patients, particularly the rare early-onset orofacial manifestations. It adds to the growing body of knowledge regarding the diverse clinical presentations of *SCN8A*-associated disorders and suggests potential avenues for clinical management and further research.

KEYWORDS

intermittent esotropia, lingual dyskinesia, movement disorders, paroxysmal strabismus, *SCN8A*, self-limiting familial infantile epilepsy

1 | INTRODUCTION

SCN8A encodes the α-subunit of voltage-gated sodium channel $Na_V1.6$, prominently expressed in cortical and subcortical structures, and pivotal in neuronal excitability. Recent years have witnessed the emergence of pathogenic *SCN8A* variants associated with a spectrum of neurodevelopmental disorders.[1] Among these, patients with Self-limiting Familial Infantile Epilepsy (SeLFIE) represent the milder end of the spectrum, characterized by self-limiting afebrile focal seizures in the first year of life, with occasional recurrences later on.[2,3] Remarkably, SeLFIE patients usually maintain normal psychomotor development and cognitive function. The frequency of this phenotype, among *SCN8A*-related conditions, was estimated to be around 6.8%.[1] This condition typically exhibits an autosomal dominant inheritance pattern within families. Furthermore, during adolescence, a subset of patients may develop paroxysmal kinesigenic dyskinesia (PKD). *SCN8A* variants associated with SeLFIE are known to confer a mild gain-of-function (GoF) effect, often leading to favorable responses to low-dose sodium channel blockers (SCB).[4]

Herein, we present the case of an infant with a missense *SCN8A* variant and SeLFIE, who also manifested paroxysmal strabismus and lingual dystonia. This case sheds light on the intriguing relationship between seizures and movement disorders in *SCN8A*-related disorders.

2 | FAMILY DESCRIPTION

The proband is a 1-year-old girl, the second child of non-consanguineous parents, born without complications following a full-term pregnancy. Family history revealed epilepsy in the maternal lineage (Figure 1A).

Regular psychomotor development progressed uneventfully until the age of 5 months, when she exhibited paroxysmal strabismus characterized by alternating esophoria, predominant in the right eye (Figure 2A). Initially, these episodes lasted a few seconds and gradually increased in frequency (several daily) and duration (minutes). Ophthalmological assessment excluded any refractive errors.

At 6 months of age, she presented with unprovoked focal onset seizures lasting 2–3 min, with head and eye deviation, apnea, hypotonia, eyelid fluttering, sometimes followed by diffuse clonic jerks. Neurological and physical examinations were unremarkable, except for the paroxysmal strabismus, which intensified after epilepsy onset. Additionally, episodes of tongue deviation, accompanied by mild dyskinetic protrusion movements lasting a few seconds, emerged without involvement of other facial muscles (Figure 2B, Viedo 1). Oral examination revealed no abnormalities of the tongue and no dental eruption; feeding and swallowing remaining unaffected. The patient did not exhibit distress or discomfort, and lingual protrusion could be interrupted by tactile stimulation or offering a spoon during feeding.

Following the administration of levetiracetam (LEV) (5 mg/kg × 2/day), she experienced several focal-to-bilateral tonic–clonic seizures (Figure 2C), followed by eye deviation and miosis lasting approximately 10 min. During this period, episodes of strabismus and tongue deviation increased in frequency and duration. Transitioning to valproic acid (VPA) resulted in seizure freedom and complete resolution of strabismus, while the episodes of tongue deviation became less prolonged and frequent.

Routine blood tests, brain CT and MRI scans yielded normal results. Trio whole exome sequencing (WES) identified a missense variant in *SCN8A* [c.4447G > A p.(Glu1483Lys)] inherited from the mother. This variant has a mild GoF effect[2]; consequently, treatment was shifted to lamotrigine (LTG). At the most recent follow-up (at 1 year old), she was seizure-free, exhibited normal development and experienced occasional brief paroxysmal tongue deviation.

Both her mother and grandmother suffered from treatable seizures during infancy that spontaneously remitted, with sporadic relapses in early adulthood. Psychomotor development and cognition were normal (Figure 1B). The mother presented with frequent bilateral tonic–clonic seizures at 9 months of age, occasionally clustering, and subsequently experienced seizures again at 1.5 years of age. Since then, VPA was introduced achieving seizure control; attempts at tapering led to seizure recurrence until 6 years of age, when VPA was successfully discontinued. From 13 to 30 years, she reported brief (few seconds) daily episodes, with tingling sensations and muscle tension in the upper limbs ("as if the right limbs were being pulled to the left"), accompanied by an internal sensation of remoteness ("as being far away in a glass box"), typically triggered by sudden movements (standing up) or stress. The episodes were captured on video-EEG and diagnosed as paroxysmal kinesigenic dyskinesia.

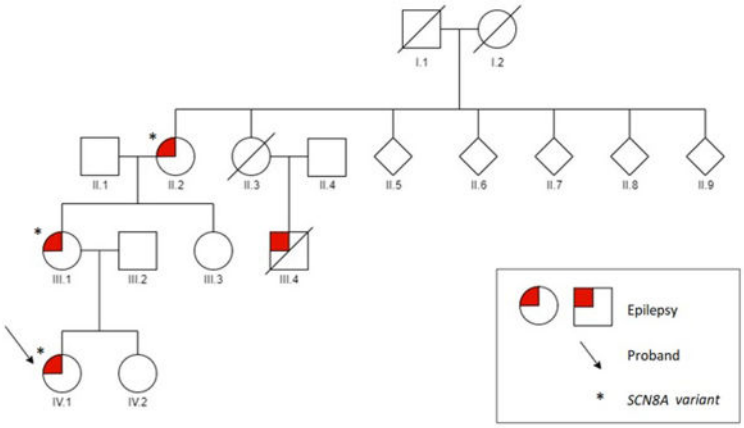
A cousin of the mother, a male with drug-resistant epilepsy and normal cognition, not genetically tested, died at the age of 35 with a potential diagnosis of SUDEP.

3 | DISCUSSION

We report the association of focal seizures, paroxysmal strabismus, and dystonic/dyskinetic movements of the tongue in an infant from a family with *SCN8A*-SeLFIE, harboring a recurrent *SCN8A* variant [c.4447G > A p.(Glu1483Lys)].[2] This variant has previously been identified in several unrelated families with *SCN8A*-SeLFIE.[2] Consistently, affected individuals within these familied exhibited infantile, self-limiting epilepsy with normal psychomotor development and cognition.

FIGURE 1 Features of the family members. (A) Family pedigree. The proband (IV.1-black arrow) as well as individuals III.1 and II.2 were tested with an epilepsy panel and harbor the SCN8A variant c.4447G > A p.(Glu1483Lys). Individual III.4, affected by unspecified epilepsy and deceased of probable SUDEP, was never genetically tested. (B) Electro-clinical features of the SCN8A family members.

(A) Family pedigree



(B) Electro-clinical features of the *SCN8A* family members

	Sex / age	Seizures (age at onset/offset)	Movement disorders (age at onset/offset)	Cognition	Current ASM (previous)	*SCN8A* variant
II.2	60 y / F	Infancy (rare relapses until 20 y)	None	Normal	None (NA)	c.4447G>A; p.(Glu1483Lys)
III.1	33 y / F	9 m / 1.5 y (rare relapses until 6 y)	Paroxysmal kinesigenic dyskinesia (13 - 30 y)	Normal	None (VPA, TPM)	
IV.1 *(proband)*	1 y / F	6 m / 7 m	Paroxysmal strabismus (5-7 m) Lingual dyskinesia (from 6 m)	Normal	LTG (LEV, VPA)	

F: female; y: years; LEV: levetiracetam; m: months; NA: not available; TPM: topiramate; VPA: valproic acid.

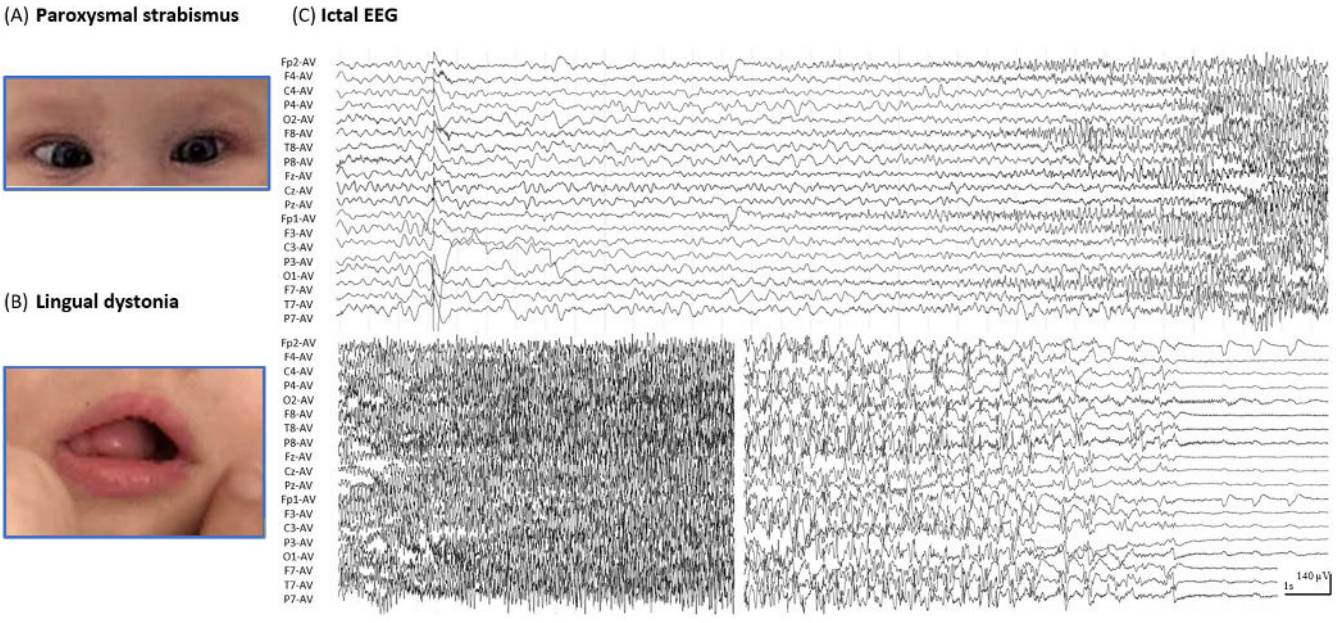
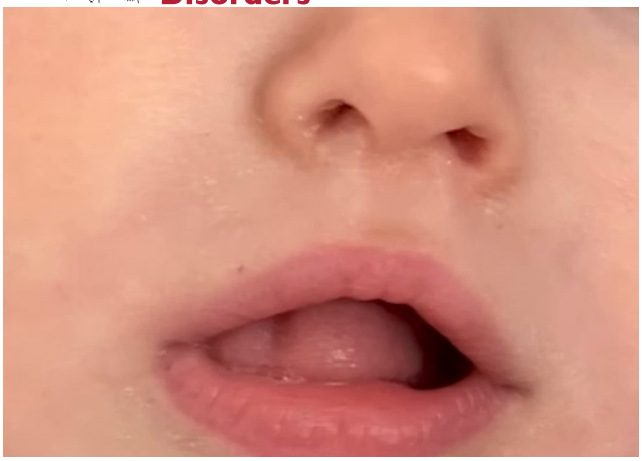


FIGURE 2 Electro-clinical features of the proband at the age of 6 months. (A) Paroxysmal strabismus; (B) Tongue dyskinesia (see also Viedo 1); (C) Ictal EEG. The EEG shows a seizure onset in the frontal and prefrontal regions, followed by diffuse spreading after 25 s. Seizures semiology consist of head and gaze deviation to the right, loss of contact, breath holding, hypotonia, eyelid flutter, and perioral cyanosis. EEG parameters: speed: 20 mm/s; sensitivity: 20 µV/mm; bandpass filter: 1–70 Hz; notch on.



VIDEO 1 Tongue dystonia (age 6 months): In the video, rightward deviation of the tongue is observed. This abnormal posture is sustained, except when the lips are touched, at which point the tongue appears to move. No fasciculation or movements of the lips, rigidity, or clonic activity in the left upper limb or associated ocular deviation/nystagmus are observed. The episode lasts for less than 20 s.

In line with SeLFIE with other etiologies,[5] a subset of individuals with *SCN8A*-SeLFIE may develop paroxysmal movement disorders during adolescence, often triggered by movement initiation or emotional stimuli.[2] The clinical course, molecular findings, and inheritance pattern in our family closely resemble those observed in the previously reported ones.[2]

Beyond seizures, our patient exhibited abnormal tongue movements and episodes of paroxysmal strabismus within the first months of life. Movement disorders represent a noteworthy, albeit underreported, feature of the *SCN8A* phenotype,[1] affecting approximately 19% of individuals.[6] We documented a novel phenomenon involving craniofacial regions in *SCN8A*-related disorders.

We excluded a range of genetically determined dystonia through WES.[7] Isolated tongue deviation can also stem from other causes such as hypoglossal nerve palsy, perinatal injuries, infections, immune-mediated or metabolic diseases, or drug administration.[7] We ruled out these potential contributing factors, strengthening the case for *SCN8A*-related lingual dystonia.

Noteworthy, the ictal involvement of the orofacial region, including the tongue, is a characteristic feature of Self-Limited Epilepsy with Centrotemporal Spikes (SeLECTS).[8] While rare, other focal seizures presenting with a "dystonic" lingual posture have been documented, albeit typically accompanied by additional clinical signs.[9] In our study, video-EEG recordings effectively excluded an ictal etiology for the observed tongue movements.

The most fitting diagnostic hypothesis for the paroxysmal tongue movements in our patient aligns with oromandibular dystonia (OMD), a specific subtype that can manifest as either task-specific or spontaneous, as observed in this case. Recent research has highlighted dystonia as a network disorder involving multiple brain regions, including the cerebellum, prefrontal and motor cortex and midbrain.[10] Tongue movements, in particular, are regulated by the inferior part of the primary motor cortex proximate to the lateral fissure, facilitated through corticobulbar connections to the lower motor neurons situated in the hypoglossal nuclei of the medulla. A recent functional MRI study has implicated alterations in regional connectivity, involving the striatum and a sensorimotor-parietal network, in focal dystonia.[11]

From a movement disorders perspective, it is important to consider the differential diagnosis of "galloping tongue," a rare lingual syndrome characterized by involuntary wave-like lingual movements. This syndrome is described in older children and adolescents, compared to the case we are presenting. Furthermore, the phenomenology differs somewhat, as it primarily involves transverse contractions, twisting, or undulating movements, especially when the patient is asked to protrude their tongue, or even at rest in most cases. This movement disorder is observed in subjects with *PRRT2* variants, that may also present with SeLFIE.[12]

Strabismus has been observed in patients with severe *SCN8A* developmental and epileptic encephalopathy (DEE).[4,13] However, less is known about its prevalence and characteristics in other *SCN8A*-phenotypic subgroups. On a contrasting note, infantile esotropia, characterized by crossed eyes in neurologically normal children during the first 6 months of life, is a common ocular motility disorder.[14] In our case, the temporal association between strabismus and seizures is intriguing. Seizures often manifest with oculomotor features, especially in children with *SCN8A*-DEE.[13] Ictal strabismus, resulting from monocular adduction, could potentially be linked to activity in the frontal eye field or occipital regions, which are involved in monocular eye movement control.[15] Significantly, in our patient, seizure onset implicated the frontal regions. The resolution of strabismus with seizure control raises the hypothesis that both phenomena might be expressions of the *SCN8A* phenotype; however, an ictal or peri-ictal origin of the strabismus episodes cannot be conclusively ruled out.

As a limitation of this case report, it is worth noting the absence of video-EEG recordings during the episodes of lingual dystonia/dyskinesia, as well as the lack of long-term follow-up data. These limitations may restrict our comprehensive understanding of the prognosis and progression of these distinctive phenotypic features. Nevertheless, this case report provides a valuable framework for researchers and clinicians in the field of developmental and epileptic encephalopathies, offering insights into atypical presentations and encouraging the expansion of diagnostic criteria for movement disorders.

In conclusion, this study broadens the *SCN8A* phenotypic spectrum by unveiling the association of early-onset paroxysmal lingual dystonia and paroxysmal strabismus in

SCN8A-SeLFIE. Recognizing this novel phenotype can facilitate early genetic diagnosis in infants with *SCN8A*-SeLFIE, enabling timely precision medicine approaches while minimizing the need for additional investigations or the suspicion of unfavorable evolution. Further cases and long-term follow-up are requisite to substantiate this observation and unravel the clinical implications of these symptoms. Additionally, an increased attention to the description of movement disorders should be extended to all early-onset epilepsies.

AUTHOR CONTRIBUTIONS

CA collected and analyzed the data and wrote the manuscript. EG conceived and designed the study, analyzed the data and revised the manuscript. JDOE and JEKN analyzed the data and edited the manuscript. MAF and FF collected the data. RSM conceived the study, and edited the manuscript. All the authors collected the data and edited the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors report no competing interests regarding this paper.

DATA AVAILABILITY STATEMENT

Anonymized data supporting the clinical report are available from the corresponding author on reasonable request. Sensitive data containing information that can compromise patient's privacy will not be publicly available.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Test yourself

1. What is the prevalence of Self-Limited Familial Infantile Epilepsy among SCN8A-related conditions?
   A. 0.5%
   B. 3.2%
   C. 6.8%
   D. 20%
2. Which antiseizure medication may be indicated in SCN8A-SeLFIE due to a gain-of-function variant?
   A. Levetiracetam
   B. Lamotrigine
   C. Vigabatrin
   D. Topiramate
   E. Ethosuximide
3. What is the most fitting diagnostic hypothesis for the tongue movements of our patient?
   A. Hypoglossal nerve palsy
   B. Drug side effect
   C. Oromandibular Dystonia
   D. Self-Limited Epilepsy with Centro-Temporal Spikes
   E. Idiopathic