Case Report

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Novel Association between SCN1A Mutation and Central Sleep Apnea: A Case of Basilar-Type Migraine

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Citation Esmaeili N, Hasani A, Saleh Nejad T, Amirifard H. Novel Association between SCN1A Mutation and Central Sleep Apnea: A Case of Basilar-Type Migraine. Case Reports in Clinical Practice. 2025; 10(1): 23-28. DOI:10.18502/crcp.v10i1.19476

Running Title SCN1A Mutation and Central Sleep Apnea in Basilar-Type Migraine

Article info:
Received: January 1, 2025
Revised: February 2, 2025
Accepted: February 21, 2025

Keywords:
SCN1A mutation; Central sleep apnea; Basilar-type migraine; Sleep disorders; Genetic mutation; Migraine pathophysiology

ABSTRACT

We report a 37-year-old woman with recurrent episodes of excessive daytime sleepiness, bizarre behavior, social delays, and confusion lasting 3–5 days. Between episodes, she experienced only mild migraine-like headaches. Genetic testing identified an SCN1A mutation, which may cause central sleep apnea, basilar-type migraine, and a channelopathy-related encephalopathic state in her.

This is the first report linking an SCN1A mutation with central sleep apnea. We recommend future cohort studies to clearly examine the association between SCN1A mutation and central sleep apnea.

Introduction

Basilar-type migraine is a rare class of migraine with aura, predominantly affecting young females [1]. Unlike the classic etiology [2], basilar-type migraine involves the vertebrobasilar circulation [1]. Accordingly, symptoms originate from the brain stem and hemispheres, including typical visual, sensory, or aphasic aura during migraine attacks [3].

The genetic predisposition is stronger in migraine with aura rather than migraine without aura [2]. Various mutations may affect migraine. For example Sodium channel NAV1.1 gene on chromosome 2 (gene symbol: SCN1A, gene id: 6323) [4].

The genetic predisposition is stronger in migraine with aura than in migraine without aura [2]. Various mutations may contribute to migraine. For example, the sodium channel NaV1.1 gene on chromosome 2 (gene symbol: *SCN1A*, gene ID: 6323) [4]. The *SCN1A* gene encodes the NaV1.1 subunit, which regulates the initiation and propagation of action potentials in neurons. Mutations in the *SCN1A* gene may lead to epileptic syndromes [5,6] and can also cause migraine [7]. An earlier study reported two cases of sudden

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infant death associated with *SCN1A* mutations [8].

Central sleep apnea (CSA) causes pauses in breathing during sleep. It occurs when the pontomedullary respiratory rhythm generator temporarily reduces or stops breathing [9]. CSA can lead to other comorbidities, such as cardiovascular dysfunction [10].

Here, we report how a mutation in the *SCN1A* gene may trigger a previously unrecognized condition—central sleep apnea—in a patient with basilar-type migraine.

Case Presentation

We report a 37-year-old woman with excessive daytime sleepiness among other symptoms. In 2021, she presented to Imam Khomeini Hospital, Tehran, Iran. The symptoms occurred in episodes lasting 3 to 5 days over several years and were associated with bizarre behavior, characterized by social delays and confusion. At times, her sleep extended up to 10 hours.

During the episodes, the patient experienced blurred vision, nausea, seizure-like attacks, and shortness of breath. She often gasped for air due to a constant sensation of suffocation; however, oxygen saturation and other vital signs remained normal. Between episodes, she did not experience the aforementioned symptoms, except for mild migraine-like headaches.

Throughout the episodes, neurological examination revealed bidirectional nystagmus, confusion, slurred speech, and alterations in the content of consciousness. Assessment of the patient's mental state was extremely difficult. Between episodes, her neuropsychiatric evaluations appeared normal.

Whole exome sequencing (WES) identified a heterozygous variant, c.1436C>T (NM_001165963.4, p.Leu479Pro), in the *SCN1A* gene. The ClinVar database classifies this variant as of unknown significance (VUS) [11]. Segregation analysis indicated paternal inheritance; however, her father is clinically asymptomatic. Supplementary genetic studies on her paternal relatives showed that none carried the variant, as demonstrated in the family pedigree (Figure 1).

We believe that this variant could be responsible for the clinical phenotypes observed in this family. It appears to follow an autosomal dominant pattern of inheritance with variable expressivity. Nevertheless,

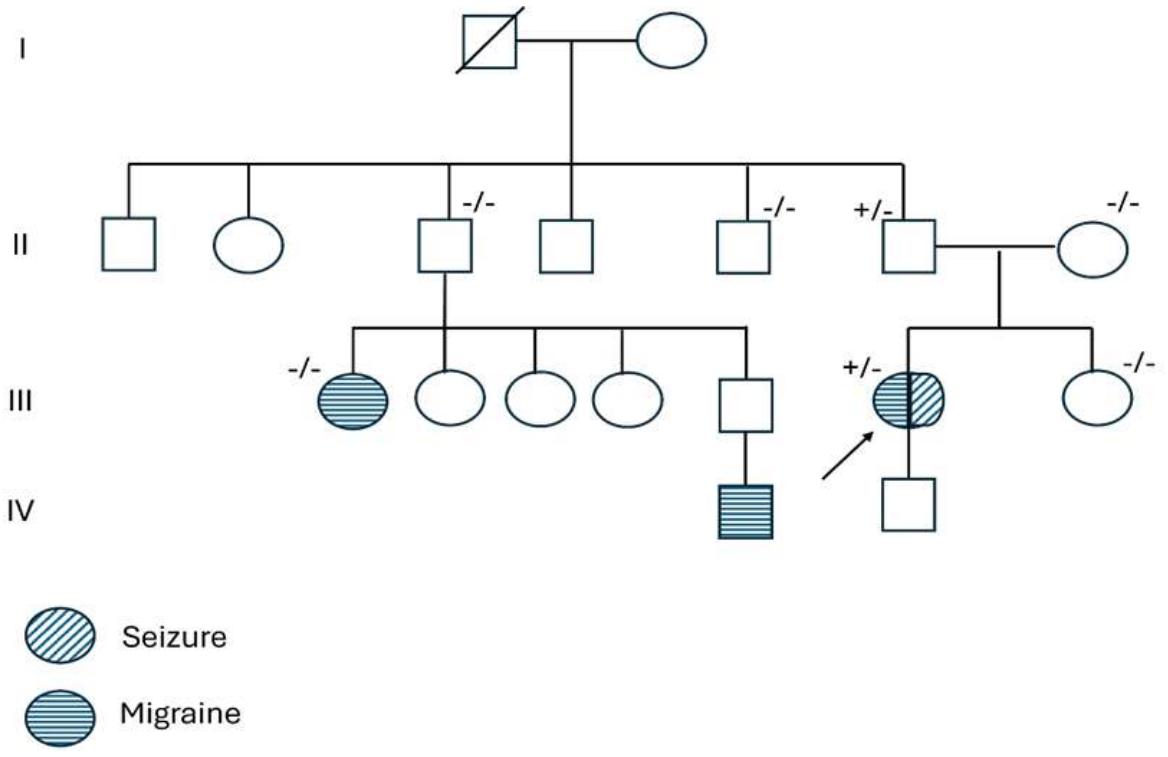

Fig. 1. Pedigree of the patient's family. The arrow indicates the proband. Striped symbols represent individuals with clinical symptoms (oblique lines for seizures, horizontal lines for migraine). The proband exhibited both symptoms, and one cousin had migraine. Positive and negative signs indicate the genotype of each individual. The proband and her father are heterozygous. (Image created using Adobe Photoshop.)

functional studies are necessary to confirm the pathogenicity of the reported variant.

The patient's final diagnosis was a combination of basilar-type migraine, channelopathy-related encephalitis, and central sleep apnea (CSA). Polysomnography confirmed CSA, which explains her sleep cycle disturbances, excessive daytime sleepiness, and respiratory symptoms during sleep. Basilar-type migraine accounts for her mild migraine-like headaches and aura symptoms.

Basilar-type migraine accounts for her mild migraine-like headaches and aura symptoms. Genetic testing revealed a mutation in the *SCN1A* gene. Previous studies have shown that mutations in this gene can cause both migraine and encephalitis [12,13], supporting our diagnostic conclusions.

We believe that the underlying channelopathy accounts for the coexistence of CSA and basilar-type migraine. This channelopathy may also precipitate an encephalopathic state during attacks, explaining the electroencephalogram (EEG) slowing, mental dullness, psychomotor slowing, unresponsiveness, and bizarre behaviors observed in this patient.

The patient underwent various therapies, including IVIG, steroid pulse therapy, and sodium valproate. Ultimately, a combination of topiramate, flunarizine, and sertraline successfully controlled her symptoms.

Brain magnetic resonance imaging (MRI) performed during the episodes appeared normal. The EEG pattern was encephalopathic, showing slowed rhythmic wave activity without any epileptiform discharges. Long-term video EEG monitoring (LTM) demonstrated generalized rhythmic delta activity (GRDA), consistent with encephalopathy, although no epileptiform patterns were observed. Figure 2 (A and B) depicts the encephalopathic pattern recorded during LTM.

A

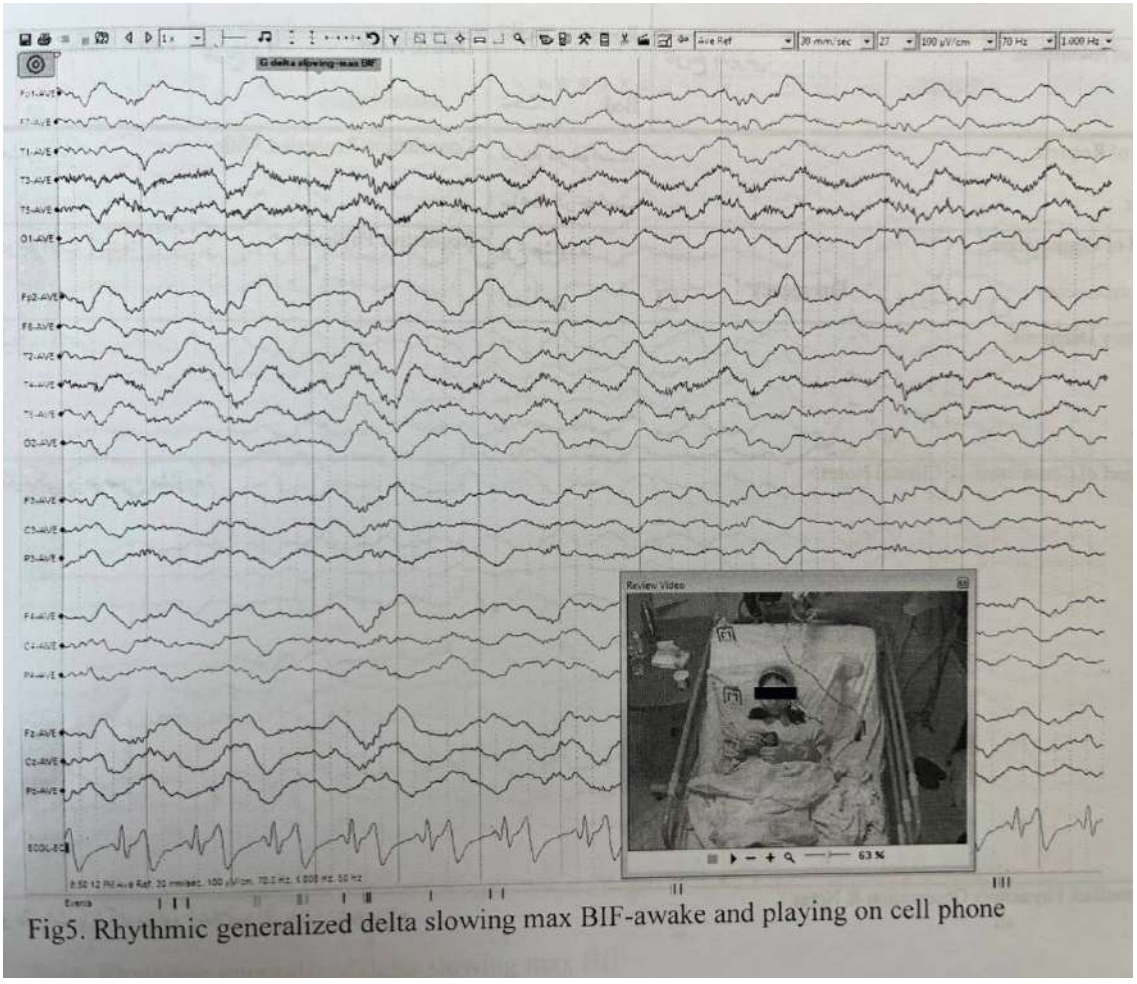

Fig. 2 (A and B). Long-term video EEG monitoring (LTM) of the patient showing generalized rhythmic delta activity (GRDA), indicative of an encephalopathic pattern. (The image was scanned from the patient's file, and all personal information was removed using Adobe Photoshop.)

B

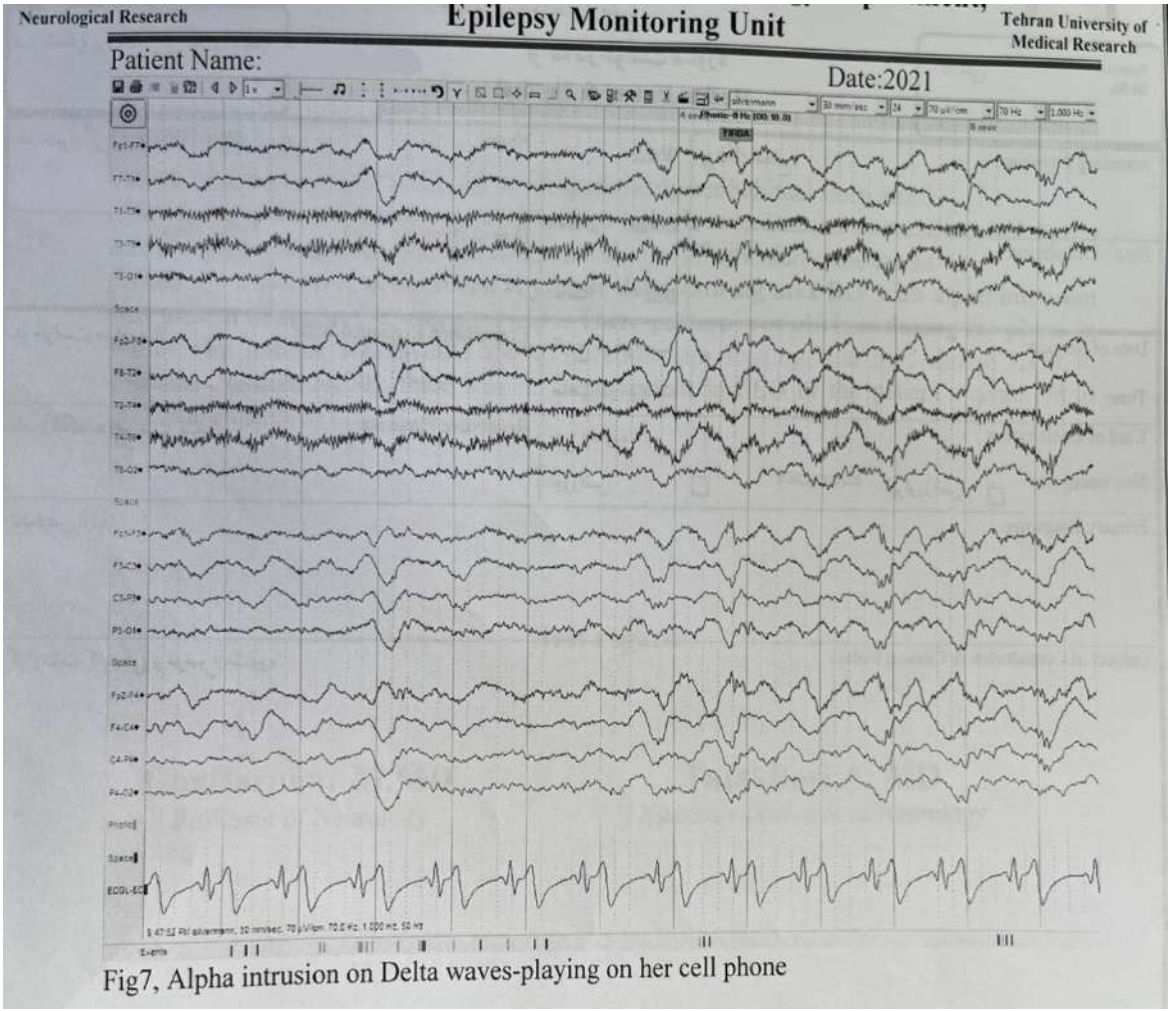

Fig. 2 (A and B). Long-term video EEG monitoring (LTM) of the patient showing generalized rhythmic delta activity (GRDA), indicative of an encephalopathic pattern. (The image was scanned from the patient's file, and all personal information was removed using Adobe Photoshop.)

Additional cardiac screenings, metabolic evaluations, and laboratory results were all within normal limits.

Polysomnography (PSG) conducted during and between episodes demonstrated an encephalopathic EEG pattern with central sleep apnea. The patient's sleep architecture was atypical, with the following distribution of sleep stages during episodes: stage 1, less than 1%; stage 2, 4%; stage 3, 95%; and no rapid eye movement (REM) sleep. The high proportion of stage 3 sleep is likely attributable to the encephalopathy in this patient. During PSG, the patient experienced 162 central sleep apneas (CSA), 14 obstructive apneas, and 3 complex apneas. The apnea-hypopnea index (AHI) was 29 events per hour, classified as moderate according to AASM criteria.

Repeat PSG performed between episodes showed different results: stage 1, 5%; stage 2, 71%; stage 3, 9%; REM, 14%; with 2 apneas and 31 hypopneas. Figure 3 illustrates the PSG during the episodes.

In summary, EEG findings, PSG results, and central apneas improved between episodes. Brain single-photon emission computed tomography (SPECT) revealed no abnormalities, helping to rule out autoimmune encephalitis.

Discussion

We report a patient with a rare combination of basilar-type migraine and central sleep apnea (CSA). To our knowledge, no previous studies have described their simultaneous occurrence, making this case important for future investigation.

The diagnosis of CSA was established based on polysomnography (PSG) findings and the patient's sleep-related symptoms.

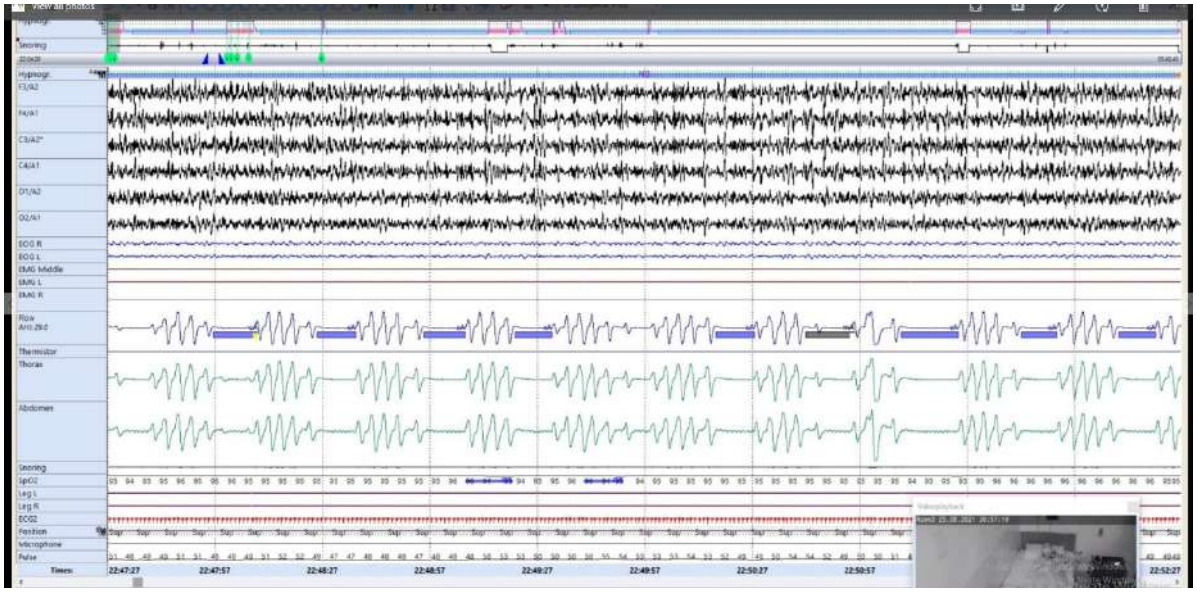

Fig. 3. Polysomnography of the patient during the attack. The PSG shows episodes of central sleep apnea (CSA) during N3 stage of sleep. (The image was scanned from the patient's file and her personal information was removed using adobe photoshop)

Bickerstaff introduced basilar migraine – a rare type of migraine – in 1961. The aura includes ataxia, vertigo, dysarthria, tinnitus, and bilateral sensory or visual symptoms.

We diagnosed basilar migraine and encephalopathy in the patient based on her neurological and behavioral symptoms. Additionally, long-term EEG monitoring (LTM) demonstrated an encephalopathic pattern.

Genetic analysis revealed a single-nucleotide mutation in the *SCN1A* gene in both the patient and her father. The *SCN1A* gene encodes a subunit of the NaV1 sodium channel, which regulates sodium influx into neurons [14]. Mutations in this gene can cause sudden death [15] or Dravet syndrome, a severe epileptic encephalopathy [12]. They are also associated with milder conditions such as hemiplegic and basilar-type migraines [13], epilepsy, and encephalopathy [12]. Although one study investigated sleep structure in children with Dravet syndrome and found no abnormalities [16], no other research has explored the link between CSA and *SCN1A* mutations.

We propose a novel association between the *SCN1A* mutation in our patient and her central sleep apnea episodes, suggesting a new potential mechanism for CSA. This case highlights the underrecognized role of the *SCN1A* gene and emphasizes the need for future cohort genetic studies to clarify the association between *SCN1A* mutations and CSA.

This is especially important given that CSA imposes a significant burden on patients and is associated with various comorbidities. Should future studies confirm this association, screening for *SCN1A* mutations in patients with CSA and unexplained neurological or behavioral symptoms may be warranted. We also recommend cost-effectiveness analyses of such screening programs.

Conclusions

Basilar-type migraine and central sleep apnea may coexist in patients with *SCN1A* mutations. We recommend future studies to investigate the association between *SCN1A* mutations and central sleep apnea.

Ethical Considerations

Ethics Statement

We took an informed consent from the patient to publish her medical documents and course of the disease.

Funding

There are no funding sources available for this report.

Conflict of Interests

None of the authors have any conflict of interest to disclose.

Consent for publication

Publication of images or other clinical details of the patient was also included in the informed consent.

Availability of data and materials

In this case report, we had no dataset. Although, after reasonable request to the corresponding author, the patient's clinical and laboratory data is accessible.

Competing interest

There are no financial and non-financial competing interests among authors and contributors.

Acknowledgements

We would like to extend our sincere gratitude to our colleagues for their invaluable contributions: Dr. L. Habibi and Dr. M. Malekian for their assistance in conducting and interpreting the genetic analysis; Dr. A. Tafakhori for performing the long-term electroencephalogram monitoring (LTM); and Dr. I. Sabzgolin for his expertise in interpreting the LTM results.

Glossary

Sodium channel NAV1.1 (SCN1A), electroencephalography (EEG) long term EEG monitoring (LTM), magnetic resonance imaging (MRI) and Polysomnigraphy (PSG), familial hemiplegic migraine (FHM), Central sleep apnea (CSA), Multiple sclerosis (MS), Intravenous immunoglobin therapy (IVIG), Rapid eye movement (REM), variant of unknown significance (VUS), single photon emission computed tomography (SPECT), American Academy of Sleep Medicine (AASM), calcium voltage-gated channel subunit alpha1 A (CACNA1A), ATPase Na+/K+ transporting subunit alpha 2 (ATP1A2), variant of unknown significance (VUS), whole exome sequencing (WES).

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