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Case Report

Acute Confusional Migraine Likely Attributed to an SCN1A Gene Mutation: A Case Report

Ahmad Hammoud[1], Tasnim K Musameh[2]*, Abdul Kareem A Abu Ali [2], Mahmoud O Jaber[2] and Marwan Assaf[2]

[1]*Department of Pediatric Neurology, Aman Lil Afia Clinic, Dubai, UAE*

[2]*College of Medicine, University of Sharjah, Sharjah, UAE*

***Corresponding Author:** Tasnim K Musameh, College of Medicine, University of Sharjah, Sharjah, UAE.

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Abstract

Background: Acute confusional migraine (ACM) is an uncommon migraine subtype marked by episodes of confusion, disorientation, and agitation, often seen in pediatric populations. It is poorly understood and frequently misdiagnosed due to overlapping features with other neurological conditions.

Case Report: In this case report, we present a 14-year-old boy who experienced recurrent episodes of confusion without headaches beginning at age 12, These episodes increased in frequency and were later triggered by physical exertion. Initial evaluations suggested migraine with aura and epilepsy, leading to trials of multiple therapies, including antiepileptic drugs and migraine prophylaxis, with limited improvement. Electroencephalographic findings during an episode revealed a pattern consistent with Frontal Intermittent Rhythmic Delta Activity (FIRDA), this pattern is often misinterpreted as seizure activity, however it has been identified as a finding in electroencephalograms in ACM cases in literature. The patient's episodes responded to valproic acid, reducing both frequency and duration. Genetic testing revealed a heterozygous Sodium Voltage-Gated Channel Alpha Subunit 1 (SCN1A) mutation, this gene encodes a sodium channel critical for neuronal excitability, and its mutations have been implicated in various neurological syndromes, but it has not yet been associated with ACM. This report is the first to propose a potential link between SCN1A mutations and ACM.

Conclusion: While ACM remains a diagnosis of exclusion, this case highlights the importance of genetic testing in complex or refractory cases, particularly in the pediatric population. Further research is warranted to explore the genetic underpinnings of ACM, potentially redefining its diagnostic and therapeutic approaches and advancing our understanding of its etiology.

Keywords: Acute Confusional Migraine; SCN1A Mutation; Familial Hemiplegic Migraine; Pediatric Neurology; Case Report

Introduction

Acute confusional migraine (ACM) is a rare and poorly understood migraine variant characterized by episodes of confusion, disorientation, and agitation, often accompanied by headache [1,2]. While ACM has primarily been reported in pediatric populations, recent cases in adolescents and adults suggest a broader clinical spectrum [3]. The etiology of ACM remains unclear, though emerging evidence points to potential genetic contributions. Notably, the SCN1A gene, which is implicated in epileptic and non-epileptic conditions such as Dravet syndrome (DS) and Familial Hemiplegic Migraine (FHM), has emerged as a candidate of interest due to its role in neuronal excitability and migraine pathophysiology [4]. Despite these associations, the specific genetic mechanisms underlying ACM remain unexplored, leaving a critical gap in understanding its pathogenesis.

This case report describes a 14-year-old male with ACM who was found to harbor a heterozygous SCN1A gene mutation. This finding offers novel insights into the potential genetic basis of ACM, drawing parallels with SCN1A-related disorders and highlighting its diagnostic and therapeutic implications. By linking this mutation to ACM, this report not only expands the phenotypic spectrum of SCN1A-related conditions but also underscores the importance of genetic screening in atypical migraine presentations. These findings contribute to a growing body of evidence suggesting that ACM may represent a distinct neurogenetic disorder, warranting further investigation into its molecular foundations.

Case Description

A 14-year-old previously healthy boy, with no history of head trauma or significant medical conditions, presented with recurrent episodes of confusion and disorientation. His first episode occurred at the age of 12, characterized by a sudden staring spell followed by confusion lasting approximately one hour, without an accompanying headache. Over the next two years, the episodes increased in frequency, progressing from once a month to several times per week. Initially, the episodes occurred spontaneously, but later, physical exertion—particularly during soccer—was identified as a trigger. As the episodes became more frequent, the patient began reporting headaches, which were not present during the initial attacks.

The hallmark of these episodes was profound confusion: the patient remained awake but was disoriented to person, time, and place. Occasionally, the episodes were associated with urinary incontinence. Initial diagnostic workup included an electroencephalogram (EEG), which showed no interictal abnormalities or background slowing, and a brain magnetic resonance imaging (MRI), which revealed a cisterna magna—a nonspecific finding of uncertain clinical significance. Based on the clinical presentation, the patient was initially diagnosed with migraine with aura and started on Topiramate. However, after three months of treatment, there was no reduction in episode frequency.

The diagnosis was subsequently reconsidered, and focal epilepsy was suspected despite the absence of interictal EEG abnormalities. The patient was started on levetiracetam, which resulted in mild symptom improvement. However, after three months, the patient developed depression, prompting discontinuation of levetiracetam and initiation of brivaracetam due to its more favorable psychiatric side effect profile. Brivaracetam reduced the duration of the episodes but did not significantly decrease their frequency. Lamotrigine was added to the regimen, but no substantial improvement was observed.

At this stage, the diagnosis of confusional migraine was reconsidered. Amitriptyline was added to the treatment plan, but the patient continued to experience weekly episodes. Long-term EEG monitoring was performed, during which an episode of confusion was captured. The EEG revealed bi-frontal rhythmic delta to theta slowing intermixed with sharp waves, consistent with Frontal Intermittent Delta Activity (FIRDA). This finding was interpreted as an epileptic phenomenon, leading to an increase in anti-seizure medications.

Seeking a second opinion, the patient was referred to our care. Upon reviewing the patient's history and video recordings of the episodes, along with the lack of response to anti-seizure medications, Psychogenic Non-Epileptic Seizures (PNES) were considered as a differential diagnosis. A 24-hour EEG with hyperventilation induction was performed, but no abnormalities were detected, and the EEG remained normal. The absence of interictal findings, combined with the patient's clinical features, made PNES unlikely. Revisiting the diagnosis of confusional migraine, we noted the patient's positive family history of migraine and reviewed literature supporting FIRDA as a potential EEG finding during acute confusional migraine episodes.

Whole Exome Sequencing (WES) was performed, revealing a heterozygous mutation in the SCN1A gene (Table 1), which is associated with Dravet Syndrome and Familial Hemiplegic Migraine (FHM). However, the patient's symptoms were inconsistent with these conditions. Given the absence of reported SCN1A mutations in acute confusional migraine, we propose that this mutation may represent a novel genetic association. The patient was started on valproic acid, a treatment option for confusional migraine, which significantly reduced the frequency and duration of his episodes.

Discussion

The diagnosis of acute confusional migraine (ACM) remains a challenge due to its nonspecific symptoms and the absence of definitive diagnostic criteria in the International Classification of Headache Disorders (ICHD-3). ACM is characterized by episodes of confusion, cortical dysfunction (e.g., speech difficulties, agitation, and amnesia), and, in some cases, headaches. Diagnosis relies on a thorough exclusion of other causes of confusion, supported by clinical history, physical examination, and diagnostic tests such as EEG and neuroimaging. However, the overlap of ACM symptoms with other neurological conditions, such as epilepsy and psychogenic non-epileptic seizures (PNES), often leads to misdiagnosis or delayed diagnosis. The lack of recognition of ACM in the ICHD-3 further complicates its identification, highlighting the need for clearer diagnostic guidelines and increased awareness among clinicians [5,6].

Gene/ID# :	SCN1A* NM_001165963 .3
Variant	c.5148C>G p.Cys1716Trp
Zygosity	Heterozygous
Disorder	Dravet Syndrome or Generalized Epilepsy With Febrile Seizures Plus, Type 2 or Migraine, Familial Hemiplegic 3
Inheritance	Autosomal Dominant
Variant Classification	Pathogenic

Table 1: Whole Exome Sequencing Showing SCN1A Gene Mutation.

*SCN1A: Sodium Voltage-Gated Channel Alpha Subunit 1.

Farooqi., *et al*. proposed the first set of diagnostic criteria for ACM, which include the presence of confusion, cortical dysfunction, and EEG findings such as Frontal Intermittent Delta Activity (FIRDA) during ictal states [1] (Table 2). FIRDA, while nonspecific and observed in various cerebral and metabolic conditions [7,8], has been reported in ACM cases during attacks, distinguishing it from epilepsy, where FIRDA typically appears in interictal or postictal periods [9]. This distinction highlights the potential utility of EEG in differentiating ACM from other conditions, particularly when combined with clinical history and symptom presentation.

(A) At least one attack, fulfilling criteria B to G, not attributed to other medical disorder and/or drug intoxication:
(B) At least one of the following:
Decreased attention
Altered awareness
Impaired cognition (disorientation and/or deficits in attention, executive function, memory)
(C) At least one of the following:
Agitation or combative behavior
Perception disturbances (i.e., visuospatial abnormalities, photophobia)
Slowing or frontal intermittent rhythmic delta activity on EEG* with complete resolution within a week
Aura (reversible visual, sensory, language or brainstem disturbance) for <1 hour (typical)
(D) Complete resolution within 24 hours or after sleep with partial or complete amnesia of event
(E) Normal neurological or no persistent neurologic deficit examination following the attack
(F) At least one of the following:
Past medical history of migraine
Family history of migraine
Headache, if present, may occur before, during and after the confusional state
(G) Not attributed to another disorder

Table 2: Proposed Acute confusional migraine diagnosis criteria by Farooqi., *et al*. [1].

*EEG: Electroencephalogram.

The etiology of ACM remains poorly understood, with minor head trauma historically considered a potential trigger. However, retrospective studies have shown that only 27-37% of ACM cases are associated with head trauma, suggesting that other factors, including genetic predispositions, may play a significant role [1,10]. This case report presents a novel association between ACM and a heterozygous SCN1A gene mutation, a finding not previously documented in the literature. The SCN1A gene, known for its role in Dravet syndrome and familial hemiplegic migraine (FHM), encodes a voltage-gated sodium channel critical for neuronal excitability [11,12].

The identified variant in our case is a heterozygous missense variant in the SCN1A gene which was classified as pathogenic based on computational evidence, conservation analysis, and its absence in control databases, supporting its potential contribution to the patient's phenotype. This variant has been classified as a Pathogenic variant by Varsome. It has not been reported in ClinVar. The variant is absent from controls in the gnomAD database (PM2). The variant is in a hotspot of 17 amino acids where a total of 31 missense and frameshift variants were detected (PM1). There is a lot of computational evidence suggesting a strongly pathogenic outlook for this variant (PP3). This includes Polyphen2, mutation taster and

SIFT. The variant is classified as disease causing, deleterious and probably damaging. The variant changes a conserved amino acid. There is also another variant that is two nucleotides away from our variant. This nucleotide change ends up changing the same amino acid of our variant but instead of changing it to a Trp it changes it to Arg. This variant was classified as Pathogenic as well by Varsome and by ClinVar (ID:68565) (PM5). The collection of evidence and the ACMG criteria suggests this variant to be a pathogenic variant. The vertebrate sodium channel is a voltage-gated ion channel essential for the generation and propagation of action potentials, chiefly in nerve and muscle. Voltage-sensitive sodium channels are heteromeric complexes consisting of a large central pore-forming glycosylated alpha subunit and 2 smaller auxiliary beta subunits. Functional studies have indicated that the transmembrane alpha subunit of the brain sodium channels is sufficient for expression of functional sodium channels. Human SCN1A is highly conserved, with 98% amino acid sequence identity to the corresponding rat sequence. Of all the known epilepsy genes, SCN1A was the most clinically relevant, with the largest number of epilepsy-related mutations characterized to that time. This variant in our case is a de novo variant, as parents of our patient were tested for the same variant and both were negative.

Moreover, adding to the challenge of ACM, the clinical management of ACM is largely empirical, with treatments often borrowed from other migraine subtypes or epilepsy. In this case, the patient's lack of response to topiramate, levetiracetam, and brivaracetam, followed by a partial response to valproic acid, stresses the complexity of managing ACM. Valproic acid, a broad-spectrum antiepileptic with migraine prophylaxis properties, was chosen based on its dual mechanism of action and its efficacy in reducing episode frequency and duration. This aligns with existing literature suggesting that medications targeting neuronal hyperexcitability may be beneficial in ACM [5].

The identification of an SCN1A mutation in this case raises important questions about the genetic basis of ACM. While SCN1A mutations are well-documented in Dravet syndrome and FHM, their association with ACM has not been previously reported. This finding suggests that ACM may represent a distinct neurogenetic disorder within the spectrum of SCN1A-related conditions. Further studies are needed to explore the prevalence of SCN1A mutations in ACM and to determine whether specific genetic variants correlate with clinical phenotypes or treatment responses.

Conclusion

The diagnosis of acute confusional migraine (ACM) remains a significant clinical challenge due to its controversial nature, incomplete phenotypic characterization, and absence from the International Classification of Headache Disorders (ICHD-3). This lack of formal recognition often leads to misdiagnoses and overlooked cases, particularly in pediatric populations. However, the identification of an SCN1A gene mutation in this case highlights the potential role of genetic factors in ACM, offering a promising avenue for improving diagnostic accuracy. Clinicians should consider routine genetic screening, including whole exome sequencing, in pediatric patients presenting with atypical or treatment-resistant confusional episodes. Additionally, developing standardized diagnostic criteria that incorporate genetic findings could significantly enhance diagnostic precision and clinical management. Such an approach could also guide personalized treatment strategies, such as the use of sodium channel modulators like valproic acid, which demonstrated efficacy in this case.

In conclusion, this case report advances our understanding of ACM by linking it to an SCN1A mutation, a finding with potential implications for both diagnosis and treatment. By embracing genetic insights and fostering targeted research, we can move closer to unraveling the complex etiology of ACM and improving outcomes for affected patients.

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Conflicts of Interest Disclosure

None declared.

Informed Consent

The patient has consented to the submission of this case to the journal.

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