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CASE REPORT

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From Asymptomatic Carrier to Severe Epileptic Encephalopathy: First Albanian Pediatric Case of Early-Onset *KCNT1*-Related Epilepsy

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Abstract

We report a pediatric case of genetically confirmed *KCNT1*-related epilepsy presenting with early-onset nocturnal frontal lobe seizures, multiple seizure types, and progressive psychomotor regression. Seizures were refractory to multiple anti-seizure medications. Trio exome sequencing identified a heterozygous *KCNT1* c.2882G>A (p.Arg961His) variant inherited from an asymptomatic father, consistent with autosomal dominant epilepsy with incomplete penetrance. This case highlights the phenotypic variability of *KCNT1*-related disorders and underscores the diagnostic, therapeutic, and genetic counseling challenges in early-onset developmental and epileptic encephalopathies.(**International Journal of Biomedicine. 2026;16(2):274-277.**)

Keywords: epileptic encephalopathy • pediatrics • KCNT1 • gene mutation

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Introduction

Pathogenic variants in *KCNT1*, which encodes a sodium-activated potassium channel (Slack channel), cause a group of rare developmental and epileptic encephalopathies (DEE) characterized by neuronal hyperexcitability due to gain-of-function channel dysfunction.[1,2] *KCNT1*-related epilepsies include early infantile epileptic encephalopathy type 14 (EIEE14; OMIM 614959) and autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE5), representing a clinical continuum ranging from severe infantile-onset encephalopathy to later-onset focal epilepsy with preserved cognition.[3,4]

KCNT1-related disorders are rare, accounting for a small proportion of genetic epileptic encephalopathies, but are increasingly recognized with the widespread use of next-generation sequencing.[5] Most affected individuals present in infancy, typically within the first year of life, with frequent nocturnal seizures, autonomic manifestations, multiple seizure types, and early pharmacoresistance.[1,6] Neurodevelopmental delay or regression is common, particularly in early-onset forms, often leading to severe motor impairment, intellectual disability, and loss of previously acquired milestones.[2,7]

To date, numerous *KCNT1* variants, predominantly missense changes, have been identified, most of which result in channel gain-of-function.[1,8] These variants exhibit marked phenotypic heterogeneity, even within the same family, with reported outcomes ranging from asymptomatic carriers to profound developmental epileptic encephalopathy.[3,9]

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Incomplete penetrance and variable expressivity pose significant diagnostic and genetic counseling challenges, particularly in autosomal dominant cases inherited from clinically unaffected parents.[4,9]

Given the overlap of clinical features with other epileptic encephalopathies and the frequent resistance to conventional anti-seizure medications, early molecular diagnosis is critical for accurate classification, prognostic assessment, and therapeutic decision-making.[5,10] Here, we report a pediatric case from Albania with severe early-onset *KCNT1*-related epilepsy and psychomotor regression, highlighting the genotype–phenotype correlation and the clinical implications of inherited *KCNT1* variants with reduced penetrance.

Case Presentation

A male child was born at 37 weeks' gestation following an uneventful pregnancy, with a birth weight of 2550 g and Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. Early postnatal development was unremarkable until 7 months of age.

At 7 months, nocturnal episodes characterized by choking and vomiting shortly after sleep onset were observed, followed by seizures with chewing automatisms occurring predominantly during sleep. Seizure frequency rapidly increased, prompting hospital admission for afebrile convulsive episodes. Initial treatment with phenobarbital showed limited efficacy. Subsequently, complex focal seizures with left-sided hemiconvulsions, secondary generalization, and autonomic features (choking, chewing automatisms) were noted, often during sleep.

Laboratory investigations revealed a mild left shift in leukocyte distribution with normal biochemical parameters. Cerebrospinal fluid analysis was unremarkable. Cranial ultrasonography and computed tomography showed no structural abnormalities. Electroencephalography demonstrated fast beta activity in the frontotemporal regions with right temporal delta waves. Cardiac evaluation and abdominal ultrasonography excluded associated systemic pathology.

Despite sequential trials of multiple anti-seizure medications, including valproate, carbamazepine, levetiracetam, topiramate, vigabatrin, clonazepam, clobazam, lamotrigine, and adrenocorticotropic hormone, seizures remained refractory. Only clonazepam provided partial and transient improvement. Seizure frequency eventually increased to 20–25 episodes per day. Evaluation at a tertiary epilepsy center, "Bambino Gesù Children's Hospital" in Rome, documented infantile spasms, leading to the addition of vigabatrin.

Neurodevelopmental regression became evident after 12 months of age. At 2 years, the child exhibited profound psychomotor impairment, including axial hypotonia with peripheral hypertonia, tetraplegia, absence of speech, poor visual tracking, feeding difficulties, and global developmental regression. Ongoing management includes polytherapy with anti-seizure medications, physiotherapy, and developmental support.

Family history revealed no reported epilepsy. However, both the father and the paternal grandmother suffered from migraine, suggesting a possible underlying familial channelopathy-related neurological vulnerability. Given the early onset, pharmacoresistance, nocturnal seizure predominance, and developmental regression, a genetic etiology was strongly suspected.

Trio exome sequencing (CentoXome® Trio, Centogene, 2021) identified a heterozygous missense variant in *KCNT1* (NM_020822.2 (*KCNT1*):c.2882G>A; p.Arg961His), classified as likely pathogenic. The variant was inherited from the father, who remains clinically unaffected, while the mother tested negative. This finding established the diagnosis of autosomal dominant *KCNT1*-related epilepsy with incomplete penetrance, accounting for the severe infantile epileptic encephalopathy observed in the proband and the absence of epilepsy in the carrier parent.

Discussion

This case illustrates a severe phenotype within the spectrum of *KCNT1*-related epilepsies, characterized by early-onset, predominantly nocturnal seizures, multiple seizure types, profound pharmacoresistance, and rapid neurodevelopmental regression. Such a clinical course is consistent with previously described *KCNT1*-associated developmental and epileptic encephalopathies (DEE), in which seizure onset typically occurs within the first year of life and is frequently resistant to conventional anti-seizure medications.[1–3]

The proband demonstrated several hallmark features of *KCNT1*-related disease, including autonomic nocturnal seizures with hypermotor manifestations, evolution to infantile spasms, and progressive loss of acquired developmental milestones. These clinical characteristics support the growing view that early infantile epileptic encephalopathy type 14 (EIEE14) and autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE5) represent a phenotypic continuum rather than distinct nosological entities.[2,4] The coexistence of focal seizures, spasms, and generalized seizure types in this patient further reflects the broad epileptic spectrum associated with *KCNT1* dysfunction.

Trio exome sequencing identified a heterozygous *KCNT1* c.2882G>A (p.Arg961His) variant inherited from an asymptomatic father, highlighting reduced penetrance and marked intrafamilial phenotypic variability. Incomplete penetrance has been repeatedly reported in autosomal dominant *KCNT1*-related epilepsies and poses significant challenges for clinical interpretation and genetic counselling.[6,9] The absence of epilepsy in the carrier parent underscores that severe epileptic encephalopathy can arise in offspring despite minimal or absent manifestations in transmitting relatives, emphasizing the limited predictive value of family history alone.

Functionally, most pathogenic *KCNT1* variants are gain-of-function missense mutations that increase potassium channel activity, leading to neuronal hyperexcitability and network instability.[1,8] Experimental studies have demonstrated that such mutations alter channel gating properties, resulting in excessive potassium currents and paradoxical enhancement of epileptogenic activity.[8] This molecular mechanism provides a plausible

explanation for the early onset, nocturnal predominance, and marked drug resistance observed in affected individuals.

Therapeutically, *KCNT1*-related epilepsies remain a major clinical challenge. Conventional anti-seizure medications are frequently ineffective, as observed in the present case, where extensive polytherapy yielded only transient or partial benefit. In recent years, quinidine, a partial blocker of *KCNT1* channels, has been investigated as a targeted treatment based on its ability to counteract gain-of-function channel activity.[11,12] However, reported clinical responses have been highly variable, with some patients showing seizure reduction and others deriving minimal benefit or experiencing dose-limiting adverse effects, particularly cardiac toxicity. [12,13] These findings highlight the need for careful patient selection, close monitoring, and further studies to define the role of precision therapies in *KCNT1*-associated epilepsy.

Beyond seizure control, neurodevelopmental outcome remains poor in severe early-onset forms, even when partial seizure reduction is achieved. Early and sustained epileptic activity, combined with intrinsic channel dysfunction, likely contributes to irreversible neurodevelopmental impairment. [3,7] This underscores the importance of early genetic diagnosis, not only to guide treatment decisions but also to provide realistic prognostic counseling and to initiate timely supportive and rehabilitative interventions.

Overall, this case expands the clinical spectrum of *KCNT1*-related epilepsy by documenting a severe early-onset phenotype with paternal inheritance and incomplete penetrance in an Albanian child. It reinforces the critical role of molecular diagnostics in refractory infantile epilepsies and highlights the complex interplay between genotype, penetrance, and clinical severity in *KCNT1*-associated disorders.

Conclusions

This report presents the first documented case from Albania of *KCNT1*-related early-onset developmental and epileptic encephalopathy with autosomal dominant inheritance and incomplete penetrance. The patient's severe and rapidly progressive clinical course highlights the broad phenotypic spectrum associated with *KCNT1* variants, ranging from asymptomatic carriers to profound epileptic encephalopathy within the same family.

This case underscores the critical role of early and comprehensive genetic testing in infants with refractory epilepsy, particularly when clinical features include nocturnal seizures, autonomic manifestations, and early neurodevelopmental regression. Establishing a molecular diagnosis is essential not only for accurate disease classification but also for prognostic assessment, informed genetic counseling, and appropriate family risk evaluation.

Furthermore, early identification of *KCNT1*-related epilepsy may facilitate timely consideration of precision-based therapeutic strategies and the initiation of multidisciplinary supportive care aimed at optimizing neurodevelopmental outcomes. Collectively, these findings emphasize the importance of integrating genetic diagnostics into routine clinical practice for severe early-onset epilepsies.

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Author Contributions

Aida Bushati: Clinical evaluation, Data curation, Writing – original draft.
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Aferdita Tako: Supervision, Conceptualization, Writing – review and editing.
All authors have approved the final article.

Conflict of Interest

The authors have declared no conflict of interest.

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Disclaimers

The views expressed in this article are those of the authors and do not necessarily reflect the official position of the affiliated institution or any funding body.

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