

Potassium channel subfamily T member 1 (KCNT1) pathological variant causing epilepsy of infancy with migrating focal seizures: a case report

Prem Chand,¹ Meher Angez,² Ayesha Nasir Hameed,³ Salman Kirmani⁴

Abstract

Pathological mutation of potassium channel subfamily T member 1 (KCNT1) gene causes an autosomal dominant disorder characterised by secondarily generalised seizures/migratory focal seizure, cyanosis, and dysmorphic features. We report the case of a five-month-old male with pathological KCNT1 variant who presented with focal clonic seizures, Mongol spots, and grade two systolic murmur at the left lower sternal border and loud P2. The seizures were refractory to most anti-epileptic drugs but showed some response to Valproic acid. This case demonstrated that EIMFS is a grave infantile epileptic encephalopathy which is refractory to anti-epileptic drugs and can present with a wide spectrum of neurogenic and cardiogenic symptoms.

Keywords: KCNT1; Mutation; Paediatric; Pakistan.

DOI: 10.47391/JPMA.6759

Submission completion date: 25-04-2022

Acceptance date: 21-12-2022

Introduction

KCNT1 gene (Potassium channel subfamily T member 1) encodes for the alpha subunit of a weakly voltage-dependent sodium-activated potassium channel also known as SLACK (sequence like a calcium activated K⁺ channel).¹ Pathological mutation of KCNT1 gene causes an autosomal dominant disorder characterised by nocturnal frontal lobe epilepsy (ADNFLE) in children and adults, an early-onset epileptic encephalopathy (EOEE) in infants and children, and the most severe form, epilepsy of infancy with migrating focal seizures (EIMFS) in neonates and infants.^{2,3} Clinical presentation of KCNT1 gene includes developmental delay, mild to moderate intellectual delay, secondarily generalised seizures/migratory focal seizure, eye deviation, bilateral twitching of eyes, frothing from the mouth, cyanosis, and dysmorphic features such as sloping forehead, long philtrum, thin upper lip and long slender fingers.^{2,4,5}

.....
^{1,4}Department of Paediatric and Child Health, Aga Khan University, Karachi, Pakistan, ^{2,3}4th Year MBBS Student, Aga Khan University, Karachi, Pakistan.

Correspondence: Prem Chand. Email: prem.chand@aku.edu

ORCID ID. 0000-0001-5401-4780

Very few cases of KCNT1 mutation have been reported worldwide. To contribute to the limited existing cases, we report the case of a five-month-old male diagnosed with epilepsy of infancy with migrating focal seizures (EIMFS) associated with KCNT1 mutation.

Case Report

Here, we report the case of a five-month-old male, carrying a pathologic KCNT-1 variant, who presented with multiple fits since the third day of birth (almost 10 to 20/day) to the Aga Khan University Hospital on April 27, 2021. Seizures were jerky movements and were of focal clonic type (lasted for 10 seconds) with bilateral twitching of the eyes, eye deviation towards right and up rolling and frothing from the mouth, and cyanosis. Ictal features such as eye deviation, bilateral twitching of the eyes, frothing from mouth, and cyanosis were seen in this patient. He is a full-term baby of a consanguineous parents, born via elective lower (uterine) segment Caesarean section (LSCS) due to previous scar and the baby had cried after two minutes of stimulation; however, neonatal course was normal. Family history was unremarkable.

Physical examination at the age of 45 days showed normal growth (Occipito-frontal circumference: 38cm, Weight: 3,200 grams [3.2kg], Height: 54cm). There was mild hepatomegaly, and the rest of systemic examination was unremarkable. Additionally, the patient did not have any dysmorphic features, except for extensive Mongol spots on his back. On examination, the patient was awake, and alert, and neurologic exam showed hypertonia and hyperreflexia. Anterior fontanelles were flat and open. Cardiovascular exam showed grade two systolic murmur at the left lower sternal border and loud P2.

Laboratory investigations showed normal thyroid function tests, calcium, C-reactive protein, lactate, lactic acid, urinary organic acids, and uric acids. The level of plasma amino acids including threonine, glutamate, glycine, and alanine were raised, while cystine, histidine, and arginine were below the normal range. The levels of blood cells and platelet counts were all in normal ranges except for red blood cells (RBCs: 2.7, Hb: 7.4, Hct: 22.4, MCV: 87.2 and MCH: 28.8). EEG showed excessive multifocal sharp transient in sleep and no active epileptic

discharges were noted. EEG revealed focal ictal discharges with varying laterality, epileptiform discharges were arising from the right parieto-temporo-occipital region later migrating to involve the left hemisphere. The MRI and ultrasound of the brain were also normal. In addition, echocardiography showed a small patent foramen ovale (PFO), mild flow acceleration across the left pulmonary artery, normal biventricular systolic function, and tiny bronchial collateral were seen.

The patient was unresponsive to first-line Phenobarbital, Levetiracetam and vitamin-D supplements and second line Topiramate and Clonazepam. Further metabolic and genetic workup was done that was suggestive of KCNT1. Valproic acid was then added to the regimen. Sleep EEG study with varying laterality: 10 second EEG epoch at sensitivity of 70uv (microvolt) showing independent right hemisphere discharges (Fig A), migrating to the left hemisphere (Fig B).

The dose of anti-seizure medication (ASMs) was increased. However, neither ASMs nor ketogenic diet (KD) could control his seizures. Currently, the child is on KD along with ASMs but his seizures are not in control and he is not achieving his milestones (global delay) according to age.

Discussion

KCNT1 gene has an autosomal dominant pattern of inheritance and encodes for the pore-forming alpha subunit of a voltage dependent sodium activated potassium channel also known as SLACK (sequence like a calcium activated K⁺ channel).² It is the largest potassium channel subunit with the highest concentration of channels in the central nervous system, particularly the frontal cortex.⁴ KCNT1 has several functions including the regulation of neuronal firing rate, slow hyperpolarisation following repetitive firing, and neuronal response to hypoxia.⁶ The first disease-causing mutation in KCNT1 was reported in 2012³ and to date several de novo mutations have been identified in children.² Functional studies have shown that mutations in the gene are mostly missense gain-of-function mutations that result in constitutional activation of potassium channels with enhanced potassium current through the channels and loss of inhibition leading to epileptogenesis.¹ Hence, pathogenic variants of KCNT1 have emerged as an important cause of epilepsy in recent years with a wide range of phenotypic spectrum: autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) in children and adults, an early-onset epileptic encephalopathy (EOEE) in infants and children, and the most severe form, epilepsy of infancy with migrating focal seizures (EIMFS) in

neonates and infants.^{7,8}

To the best of our knowledge, this is the first case of KCNT1-associated epilepsy from Pakistan. Epilepsy of infancy (EIMFS) is a rare calamitous epileptic encephalopathy and to date only around 100 patients have been reported worldwide with half of them having KCNT1 mutations.² The present report describes a five-month-old male with generalised tonic clonic seizures since third day of birth. Data from previous studies in USA report the mean age of seizure onset to be < 6 months (EIMFS, 97%) with secondarily generalised seizures being the most common type (EIMFS, 57%).⁶ Case reports from Asian countries such as India and Japan report an even earlier age of onset of two months and mostly epileptic spasms or focal seizures.^{2,4}

No statistically significant relation with gender has been established so far. Our findings show a mixed pattern with the age distribution more similar to data from Asian population, while type of seizure is consistent with features seen in studies from USA. Ictal features such as eye deviation, bilateral twitching of the eyes, frothing from the mouth, and cyanosis seen in this case correspond with features observed in previously reported cases that describe night-time 'gagging spells'⁵ eye deviation, and episodes of apnoea in patients.⁴ In this case of KCNT1 mutation, the child had normal growth and development with timely achievement of all milestones. This is a new finding in comparison to many previously reported cases from other populations which show a mental developmental regression and psychomotor retardation from early infancy.⁹ Presentation of KCNT1-associated epilepsy from Asian countries revealed subtle dysmorphism amongst affected individuals with features such as sloping forehead, long philtrum, thin upper lip, and long slender fingers.² Our case differs in these findings with the patient presenting with no dysmorphic features except for extensive Mongol spots on the back. However, findings such as normal anthropometric measurements are consistent with previous literature. The presence of grade II systolic murmur at left lower sternal border and loud P2 in our patient can be explained by the fact that the potassium channels that are over-activated as a result of KCNT1 mutation are also largely present on cardiomyocytes. This also explains the use of quinidine—an anti-arrhythmic drug—in the treatment of KCNT1 related epilepsy.⁵

One of the key features of EIMFS is its refractoriness to treatment rendering this type as the most fatal. For patients with KCNT1 related EIMFS, the most commonly prescribed therapies are Levetiracetam (96 percent), Phenobarbital (96 percent), Ketogenic diet (93 percent),

Topiramate (79 percent), and Valproic acid (68 percent).⁶ In our case, therapy with Phenobarbital, Topiramate, Levetiracetam, and Clonazepam did not yield any results. Similar type of unresponsiveness to treatment has also been noted in other cases.⁵

Conclusion

This is the first genetically confirmed case of KCNT1 mutation reported from Pakistan. We infer from this case that EIMFS is a grave infantile epileptic encephalopathy which is refractory to anti-epileptic drugs and can present with a wide spectrum of neurogenic and cardiogenic symptoms.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

References

1. Madaan P, Jauhari P, Gupta A, Chakrabarty B, Gulati S. A quinidine non responsive novel KCNT1 mutation in an Indian infant with epilepsy of infancy with migrating focal seizures. *Brain Dev* 2018;40:229-32. doi: 10.1016/j.braindev.2017.09.008.
2. Kravetz MC, Viola MS, Prenz J, Curi M, Bramuglia GF, Tenenbaum S. Case Report of Novel Genetic Variant in KCNT1 Channel and Pharmacological Treatment With Quinidine. *Precision Medicine in Refractory Epilepsy. Front Pharmacol* 2021;12:e648519. doi: 10.3389/fphar.2021.648519.
3. Cornet MC, Cilio MR. Genetics of neonatal-onset epilepsies. *Handb Clin Neurol* 2019;162:415-33. doi: 10.1016/B978-0-444-64029-1.00020-5.
4. Mori T, Imai K, Oboshi T, Fujiwara Y, Takeshita S, Saito H, et al. Usefulness of ketogenic diet in a girl with migrating partial seizures in infancy. *Brain Dev* 2016;38:601-4. doi: 10.1016/j.braindev.2015.12.012.
5. Fukuoka M, Kuki I, Kawawaki H, Okazaki S, Kim K, Hattori Y, et al. Quinidine therapy for West syndrome with KCNT1 mutation: A case report. *Brain Dev* 2017;39:80-3. doi: 10.1016/j.braindev.2016.08.002.
6. Fitzgerald MP, Fiannacca M, Smith DM, Gertler TS, Gunning B, Syrbe S, et al. Treatment Responsiveness in KCNT1-Related Epilepsy. *Neurotherapeutics* 2019;16:848-57. doi: 10.1007/s13311-019-00739-y.
7. Møller RS, Heron SE, Larsen LH, Lim CX, Ricos MG, Bayly MA, et al. Mutations in KCNT1 cause a spectrum of focal epilepsies. *Epilepsia* 2015;56:e114-20. doi: 10.1111/epi.13071
8. Ishii A, Shioda M, Okumura A, Kidokoro H, Sakauchi M, Shimada S, et al. A recurrent KCNT1 mutation in two sporadic cases with malignant migrating partial seizures in infancy. *Gene* 2013;531:467-71. doi: 10.1016/j.gene.2013.08.096.
9. Mikati MA, Jiang YH, Carboni M, Shashi V, Petrovski S, Spillmann R, et al. Quinidine in the treatment of KCNT1-positive epilepsies. *Ann Neurol* 2015;78:995-9. doi: 10.1002/ana.24520.