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Case Report

A quinidine non responsive novel KCNT1 mutation in an Indian infant with epilepsy of infancy with migrating focal seizures

Priyanka Madaan, Prashant Jauhari, Aparajita Gupta, Biswaroop Chakrabarty, Sheffali Gulati *

Child Neurology Division, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India

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Abstract

Epilepsy of infancy with migrating focal seizures {a.k.a malignant migrating partial seizures of infancy (MMPSI)} is an uncommon epileptic encephalopathy with a poor prognosis. Migrating focal seizures with autonomic features, developmental stagnation and refractoriness to treatment are its key features. It is caused by genetic defects in various ion channels, most common being sodium activated potassium channel (KCNT1), found in up to 50% of cases. With advent of genetic diagnosis and precision medicine, many targeted therapies have been identified. Antagonist of KCNT1 coded ion channel like Quinidine has shown promising results in MMPSI. Here we report first mutation proven case of MMPSI from India. This child had a novel heterozygous missense mutation in exon10 of the ***KCNT1*** gene **(chr9:138650308;** c.808C > C/G **(p.Q270E))** which was pathogenic. Neither quinidine nor ketogenic diet could control his seizures. Ultimately, the child succumbed to his illness at nine months of age.

Keywords: MMPSI; KCNT-1 gene; Quinidine; Ketogenic diet; Infantile epileptic encephalopathy

1. Introduction

Epilepsy of infancy with migrating focal seizures {a.k.a malignant migrating partial seizures of infancy (MMPSI)} is a rare early-onset infantile epileptic encephalopathy with an abysmal prognosis [1]. It is characterized by refractory migrating focal seizures, typically associated with autonomic features, clustering after awakening or while falling asleep. These children also have developmental stagnation, acquired microcephaly and gastrointestinal dysmotility. KCNT-1 mutations are seen in up to 50% of affected patients [2]. Other pathogenic genes include SCN1A, SLC25A22 and PLCB1.

KCNT1 gene (9q34.1) codes for a sodium-gated potassium channel (SLACK, SLO2.2 or KCa4.1). Mutations in this gene lead to enhanced potassium currents through the channel, resulting in epileptogenesis. Multiple de novo mutations in KCNT1 have been identified in children with MMPSI and autosomal dominant nocturnal frontal-lobe epilepsy. Quinidine is effective in about half of such patients with MMPSI [3]. Response to quinidine depends on drug levels in brain, age at initiation and prior neuronal injury due to seizures. It might also be affected by underlying genotype. We report an infant with MMPSI who had a novel heterozygous autosomal dominant mutation in KCNT1 gene.

* Corresponding author at: Child Neurology Division, Department of Pediatrics, Room No. 3056, Third Floor, Teaching Block, All India Institute of Medical Sciences, New Delhi, India.
E-mail address: sheffalig@yahoo.com (S. Gulati).

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2. Case report

Two months old baby boy, 2nd issue of non-consanguineous healthy parents, presented with intractable seizures since day 3 of life. Baby was born at term through caesarean section. Mother had past history of three first-trimester abortions. She was a carrier of 1:16 balanced translocation. The index child developed focal seizures, multiple times a day with varying laterality. There was ictal clustering with frequent seizures (up to 10/day) occurring for 3–4 days followed by a seizure free interval of 4–5 days. Before coming to our hospital, he had already failed trials of vitamins and multiple antiepileptic drugs at maximal doses (Table 1).

At presentation, physical examination revealed subtle dysmorphism (sloping forehead, long philtrum, thin upper lip and long slender fingers) with normal anthropometric indices (OFC: 37 cm, Wt: 3.8 kg and length: 55 cm) and neurological examination. A working diagnosis of early-infantile epileptic encephalopathy, probably MMPSI, was kept. Video EEG revealed focal ictal discharges with varying laterality (Fig. 1) consistent with diagnosis of MMPSI. Other investigational details are provided in Table 2. Clinical exome sequencing of the child revealed a heterozygous missense mutation in exon10 of ***KCNT1*** gene **(chr9:138650308;** c.808C > C/G **(p.Q270E))**. This mutation was further validated using Sanger sequencing. This mutation was not present in unaffected parents indicating that this was likely pathogenic (Fig. 2).

During hospital stay, baby continued to have intractable seizures with autonomic phenomena like-excessive drooling, tachycardia and tachypnea. At three months of age, baby was started on ketogenic diet (KD) (maximum ratio of 3.5:1). KD was however stopped after six weeks due to non-responsiveness and hyperuricemia requiring allopurinol. A trial of quinidine (initiated at low dose-10 mg/kg/day in three divided doses) was given at around 6 months of age after holter monitoring. It was hiked over next one week to maximum dose (35 mg/kg/day) and continued for a month but without any appreciable reduction in seizure frequency (Fig. 3).

Table 1
Antiepileptic and other relevant drugs used in the index case.

Drug	Maximal dose (mg/kg/day)	Duration	Reason for discontinuation
Phenytoin	8	3.5 months	No response, drug interaction
Phenobarbitone	5	3.5 months	No response, drug interaction
Valproate	50	8 months	Hyperammonemia: treated with oral carnitine
Levetiracetam	60	9 months	–
Topiramate	8	8 months	Hyperammonemia: treated with oral carnitine
Zonisamide	8	7 months	–
Vigabatrin	150	4 months	–
Clonazepam	0.15	9 months	–
Ketogenic diet	Ratio: 3.5:1	6 weeks	Hyperuricemia, Intolerance, pneumonia and no response
Pyridoxine	15	2 weeks	No response
Pyridoxal phosphate	20	1 week	No response
Folinic acid	5 mg twice a day	1 week	No response
Quinidine	35 mg/kg/day	1 month	Prolonged QTc interval

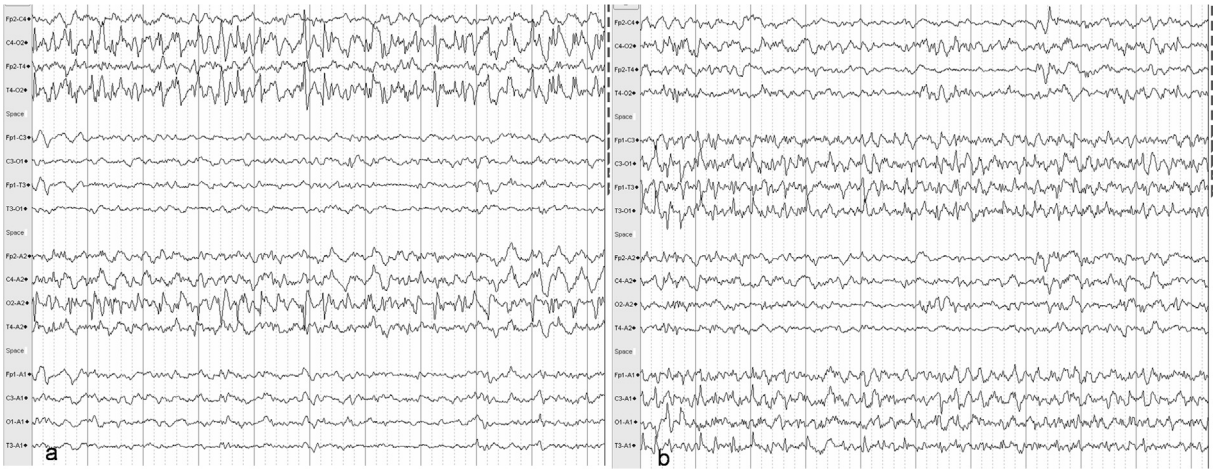

Fig. 1. Sleep EEG of the index child: Legend: 10 s EEG epochs during the same record (children montage at sensitivity: 70 μV and sweep speed: 30 mm/s) showing independent right hemispheric discharges (a) migrating to left hemisphere (b).

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