Quinidine Trial in a Patient with Epilepsy of Infancy with Migrating Focal Seizure and KCNT1 Mutation

Epilepsy of infancy with migrating focal seizures (MFEI) is an early-onset epileptic encephalopathy characterized by randomly migrating focal seizures and psychomotor deterioration. It is associated with mutations in a variety of genes, with potassium sodium-activated channel subfamily T member 1 (KCNT1) being an example. Previously reported KCNT1 mutations in MFEI are gain-of-function mutations. Therefore, quinidine therapy targeted at reduction of pathologically increased KCNT1 channel-mediated potassium conductance has been proposed as a target treatment for MFEI with KCNT1 mutation. The authors report a case involving a patient with MFEI and a missense mutation in KCNT1 (c.7129G>A; p.Phe346Leu) treated with quinidine therapy. Seizure activity was poorly responsive to quinidine.

Key Words: Epilepsy of infancy with migrating focal seizure, KCNT1 mutation, Quinidine

Introduction

Epilepsy of infancy with migrating focal seizures (MFEI) is a rare, early onset epileptic encephalopathy characterized by pharmacoresistant epilepsy and arrest of psychomotor development in the first 6 months of life. Interictal electroencephalography (EEG) demonstrates multifocal spikes and slowing, with ictal EEG discharges arising from various areas of both hemispheres and migrating from one brain region to another.

Several genetic causes of MFEI have been identified, including mutations in the potassium sodium-activated channel subfamily T member 1 (KCNT1), phospholipase C beta 1 (PLCB1), sodium voltage-gated channel alpha subunit1 (SCN1A), solute carrier family 25 member 22 (SLC25A22), and TBC1 domain family member 24 (TBC1D24). More recently, de novo mutations in the KCNT1 gene (also known as Sla2.2 or Slack) were described as disease-causing in approximately 40% to 50% of all MFEI patients. Mutations result in KCNT1 channel gain of function. Importantly, reported KCNT1 mutations in MFEI are gain-of-function mutations leading to constitutive activation of the channel; therefore, pharmacological inhibition of KCNT1 is a potential therapeutic target.

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In this report, we describe a patient with MFEI and KCNT1 mutation (c.7129G>A; p.Phe346Leu) who underwent a trial of quinidine.

**Case report**

A 3-month-old boy was admitted to our hospital via the emergency center for 5 generalized tonic seizures that lasted 1 min to 2 min for 1 day. He was first child from nonconsanguineous Korean parent; He was born at fullterm and weighted 2.6 kg. There was no family history of seizures or other neurological disorders. EEG demonstrated clinical and subclinical seizures associated with ictal discharges arising independently from the left frontal, left temporal, or right temporal areas. Brain magnetic resonance imaging revealed no abnormal findings. EEG demonstrated a pattern of MFEI; with focal seizures migrating between left and right hemispheres (Fig.1). Therefore, the patient was started on antiepileptic drugs (AEDs).

Trials of multiple medications alone and in various combinations, including phenobarbital, levetiracetam, phenytoin, topiramate, valproic acid, gabapentin, and clobazam, were without effect on seizure frequency, and the patient continued to have the patient has daily seizures of tonic seizures involving the left, right, or both sides of the body, 10 to 20 times a day, and about 1 or 2 of these seizures last longer than 20 minutes and required intravenous injection of benzodiazepine or other AEDs. When placed on continuous EEG monitoring, subclinical seizures were also frequently detected. A ketogenic diet was also attempted but was, however, abandoned after 2 months due to lack of efficacy.

Metabolic and imaging work-up were negative. A gene panel was sent out for epileptic encephalopathy, and revealed that the patient had a heterozygous mutation in the KCNT1 (c.7129G>A);

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![Figure 1](http://www.cns.or.kr)

**Fig. 1.** Electroencephalogram at initial presentation (ictal phase) Electroencephalogram at initial presentation. (A) Focal seizure originating from right temporal lobe. (B) Several seconds later, seizure has migrated to the left, clinically presenting as desaturation, vacant staring with eyeball fixation, sometimes with both arm elevation, which are associated with ictal rhythmic discharges evolving from Rt. temporal (10 times) or Lt. temporal (13 times) areas, and then spreading to ipsilateral diffuse hemisphere, sometimes spreading to whole brain.
p.Phe346Leu). His parents were also tested; however, they did not carry such a mutation, confirming that the mutation of KCNT1 gene in the patient was a *de novo* mutation (Fig. 2).

After genetic diagnosis of KCNT1 encephalopathy, quinidine therapy was attempted. He was started on 11 mg/kg/day of quinidine with gradual dose increase to 54.2 mg/kg/day (320 mg/day), but was stopped after 10 days of trial due to lack of response and tremor that appeared to be a side effect (Table 1).

To date, the patient (now 20 months old) experiences tonic seizures of either or both sides of the body 10 to 20 times per day, with approximately 1 or 2 of these seizures lasting longer than 20 min and requiring adjuvant rectal benzodiazepine injections in addition to 4 oral AEDs (barbiturate, levetiracetam, stitipentol, topiramate). The head circumference of the patient was normal (42 cm, 50 percentile) at the onset of disease, but now it is microcephaly (45 cm, <3 percentile). He has exhibited profound developmental regression since the onset of these seizures.

### Discussion

We report a case involving a patient with MFEI and mutation in KCNT1, who demonstrated no response to quinidine therapy. The identification of KCNT1 mutations as a genetic cause for MFEI and autosomal dominant nocturnal frontal lobe epilepsy suggests that these conditions may be treatable using a drug that specifically targets the KCNT1 channel. Quinidine therapy has been introduced as a targeted therapy in MFEI with KCNT1 mutation to reduce increased KCNT1 channel-mediated potassium conductance. KCNT1 encodes the pore-forming alpha subunit of the potassium channel; quinidine acts to block pores. Therefore, quinidine is a potential therapeutic agent for individuals with KCNT1 mutation.

Previous studies have demonstrated that quinidine reduces the conductance of the activated channel by a gain-of-function mutation of KCNT1 in vitro. Additionally, quinidine treatment has been trialed in three patients with KCNT1 mutations for whom treatment with standard antiepileptic therapies had been unsuccessful. Two patients with malignant migrating focal seizures of infancy experienced marked improvement in seizure control following quinidine administration. However, our patient did not experience the same effect as in vitro studies or other clinical cases.

There are several reasons why quinidine is not effective against the KCNT1 mutation when applied to actual patients. The first is that the exact concentration of quinidine needed to be effective in the brain is unknown. KCNT1 is highly expressed in both neurons and cardiomyocytes in which quinidine acts as an effective antiarrhythmic agent. However, previous studies have shown that quinidine does not accumulate well in the cerebrospinal fluid, and that levels change with interactions with AEDs. Thus, quinidine levels in the brains of patients taking AEDs may be lower than serum levels of those taking it to treat arrhythmias. However, it remains unclear whether quinidine can pass the blood-brain barrier and what levels are effective once it

| Day 1-3 | 11 mg/kg/day | 0.6 µg/mL | 10 |
| Day 4-6 | 40 mg/kg/day | 2.4 µg/mL | 13 |
| Day 7-10| 54.2 mg/kg/day| 1.7 µg/mL | 8 |

**Table 1. Timeline of Treatment**
has reached the brain, QT prolongation may occur due to the side effects of quinidine, which makes it difficult to determine an appropriate level because quinidine cannot be tried in unlimited doses until it becomes effective. Second, MFEI patients with KCNT1 mutations who undergo quinidine trials have already failed many conventional AEDs. Most are taking multiple AEDs, which can also affect quinidine levels. In addition, because seizures have been intractable for a certain period of time, it is likely that morphological changes have already occurred in the brain, regardless of the presence of KCNT1 mutation. Third, because phenotype and genotype are not always consistent, unlike previous reports describing the effectiveness of quinidine for MFEI, it may not have been effective in our patient. It is necessary to confirm that the treatment for the mutation in the genotype applies to the phenotype.

The isolation of human induced pluripotent stem cells (iPSCs) offers a novel strategy for modeling human disease, recent studies have reported the derivation and differentiation of disease-specific human iPSCs. Therefore, iPSCs may represent a possible investigative avenue in this disease model. It is also possible to perform experiments in an animal-based model with KCNT1 using gene editing through clustered regularly interspaced short palindromic repeat (CRISPR)-Cas9 technology. Seizure frequency in our patient was not decreased by quinidine therapy. In conclusion, this case suggests that quinidine is not always an effective treatment for individuals with epilepsy of infancy with migrating focal seizures and KCNT1 mutation. To tailor therapy to genetic mutations in patients, therefore, it will be necessary to conduct preliminary studies on how genotypes are actually expressed as phenotypes. Further studies are necessary to investigate exact effective doses and serum levels for the use of quinidine in patients with KCNT1 mutation, and to study whether the effect will be different when using preemptive targeting agents in addition to conventional AEDs.

요약
영아이동성 부분 발작 뇌전증(MEFI)은 여러 부위에 무작위적으로 발생하는 이동성 부분 발작과 발달이상을 특징으로 하는 조기 발병 뇌증이다. 이는 다양한 유전자의 돌연변이와 연관되어있고 그 중 하나로 KCNT1 돌연변이가 있다. 이전 연구에 따르면 MEFI의 KCNT1 돌연변이는 기능하복 돌연변이로 알려져 있다. 따라서 KCNT1 돌연변이를 가진 MEFI 환자의 표적 치료로서 병적으로 증가된 KCNT1 채널 체계 활성화 진도성의 감소를 일으키는 퀴니딘 치료가 제안되었다. 이 증례에서는 KCNT1 유전자 결실 돌연변이 (c.7129G → A; p. Phe346Leu)가 MEFI 있는 환자에게 퀴니딘 치료를 시도하여 보고하는 바이다. 특히 출생력 기저력 및 가족력 없는 환아로 생후 3개월에 발생한 전신 긴장성 발작을 주소로 내원하였다. 시행한 뇌파에서 왼쪽 후두엽, 오른쪽 후두엽 및 왼쪽 전두엽 부위에서 이동성으로 편측 발에서 발생하는 간질과 요양을 보여 영아이동성 부분 발작 뇌전증으로 진단되었으며, 푸른바비탈리, 레티리케타민, 페니토인, 토피랄암, valproic acid, gabapentin, clobazam 등의 AED를 사용하였으나 발작빈도에 변화가 보이지 않았으며, 푸른생성식이 2달간 시도하였으나 이 또한 발작빈도에 영향을 주지 않았다. 이 환자에서 KCNT1 결실 돌연변이가 있음을 유전자가 검사를 통하여 확인하여 이에 대한 표적치료로 퀴니딘을 사용하였으며 발작빈도에 미미한 영향을 주었으나, 진진등의 부작용이 발생하여 사용을 중단하였다. 현재 약물 복용을 지속하며 간헐적으로 직장으로 diazepam을 주입하여 경련을 조절 중이다. 영아이동성 부분 발작 뇌전증에서 퀴니딘 치료가 모든 환자에서 효과가 있는지 확인을 위한 선행연구가 필요할 것으로 생각된다.

References