Original article

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Quinidine therapy and therapeutic drug monitoring in four patients with *KCNT1* mutations

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ABSTRACT – *Aims*. Several recent studies have reported potassium sodium-activated channel subfamily T member 1 (*KCNT1*) mutations in epilepsy patients on quinidine therapy. The efficacy and safety of quinidine for epilepsy treatment, however, remains controversial.
Methods. We herein report the cases of four patients with *KCNT1* mutations treated with quinidine.
Results. A reduction in seizures of more than 50% after quinidine treatment was observed in one patient with epilepsy of infancy with migrating focal seizures (EIMFS), whereas two patients with EIMFS and one with focal epilepsy did not achieve apparent seizure reduction. The relationship between quinidine dose and serum quinidine concentration was inconsistent, particularly at high quinidine doses. One patient with EIMFS developed ventricular tachycardia the day after an increase in quinidine dose from 114 to 126 mg/kg/day. The serum trough quinidine concentration and the corrected QT interval (QTc) before arrhythmia onset were 2.4 μg/ml and 420 ms, respectively, and peak serum quinidine concentration after arrhythmia onset was 9.4 μg/ml. Another patient with EIMFS showed aberrant intraventricular conduction with a quinidine dose of 74.5 mg/kg/day and a serum trough concentration of 3.2 μg/ml.
Conclusions. Given that serum quinidine levels may elevate sharply after a dose increase, careful monitoring of electrocardiographs and serum concentrations is required. Based on a review of previous reports and our experience with this case, quinidine should be considered as a promising

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drug for patients with EIMFS harbouring *KCNT1* mutations, however, its efficacy remains controversial due to the limited number of cases, and more information on optimal serum concentrations and appropriate titration methods is required.

Key words: *KCNT1*, EIMFS, quinidine, serum concentration, arrhythmia, migrating focal seizures

Potassium sodium-activated channel subfamily T member 1 (*KCNT1*) encodes a sodium-activated potassium channel that is highly expressed in the central nervous system (Bhattacharjee *et al*., 2002; Bhattacharjee and Kaczmarek, 2005). KCNT1 contributes to neuronal excitability and subsequent firing as well as modulation of the resting membrane potential (Bhattacharjee *et al*., 2005). The precise functions of KCNT1, however, remain unclear. *KCNT1* mutations have been described in 39-50% of patients with epilepsy of infancy with migrating focal seizures (EIMFS) (Ohba *et al*., 2015; Lim *et al*., 2016) and in less than 5% of patients with autosomal dominant nocturnal frontal lobe epilepsy (Heron *et al*., 2012).

Recently, several studies have reported patients harbouring *KCNT1* mutations with intractable epileptic seizures who received quinidine treatment (Bearden *et al*., 2014; Mikati *et al*., 2015; Chong *et al*., 2016; Fukuoka *et al*., 2017; Abdelnour *et al*., 2018; Madaan *et al*., 2018; Mullen *et al*., 2018). Although accumulating data from multiple cases have enabled the elucidation of prognostic factors in patients with EIMFS, such as the type of epilepsy and the age at which quinidine is administered, few studies have investigated serum quinidine levels and association between serum quinidine concentration and other antiepileptic drugs that might hinder quinidine, such as phenobarbital in these patients.

Given that quinidine is one of the few drugs with potential as a treatment for patients with *KCNT1* mutations and EIMFS, determining optimal serum quinidine concentration is essential for its safe and effective use. In this report, we present the cases of four patients harbouring *KCNT1* mutations who developed seizures and were treated with quinidine, with the aim of elucidating its efficacy and utility.

Case reports

Patient 1

Patient 1 was a 20-month-old male born at 39 weeks of gestation without distress after *in vitro* fertilisation and embryo transfer. He developed focal seizures comprising asymmetric tonic posturing with eye deviation at one month of age and was diagnosed with EIMFS based on seizure symptoms and migrating foci on ictal EEG. His seizures were unresponsive to phenobarbital, clonazepam, clobazam, levetiracetam or potassium bromide. Whole-exome sequencing revealed a *de novo* heterozygous mutation in *KCNT1* (c.1283G>A: p.Arg428Gln).

The patient was administered quinidine at a starting dose of 2 mg/kg/day at the age of nine months. Cardiological evaluation prior to quinidine administration, including Holter electrocardiography (ECG), echocardiography, and chest X-ray by a paediatric cardiologist, revealed no abnormalities. The antiepileptic drugs used in combination with quinidine were levetiracetam (48 mg/kg/day) and potassium bromide (44 mg/kg/day). Although the dose of quinidine was increased gradually, the frequency of seizures did not change significantly for approximately five months. Six months after the initiation of quinidine therapy, the patient developed ventricular tachycardia and a cluster of focal tonic seizures the day after the increase in quinidine dose from 114 mg/kg/day to 126 mg/kg/day. The peak serum quinidine concentration at the time of the arrhythmic event was 9.4 μg/ml. The corrected QT interval (QTc), which was 362 ms before the initiation of quinidine therapy, was longer at 420 ms during a quinidine dose of 114 mg/kg/day. Arrhythmia disappeared following a reduction in quinidine dose to 73 mg/kg/day. Thereafter, a mild decrease in seizure frequency was observed despite no changes in medication. The average seizure frequency during the three months before the initiation of quinidine therapy was 43.3 times/day, and was 62.4% lower at 16.3 times/day during the last three months (*figure 1A*).

The relationship between serum quinidine concentration and quinidine dose, based on peak and trough levels, is shown in *figure 2A*. Briefly, there was a limited association between the trough level and dose, however, the peak quinidine level was not associated with quinidine dose between 40 and 50 mg/kg/day.

Patient 2

Patient 2 was a three-year-old female born at term without distress. Her first seizure occurred at two months of age, and her seizures comprised asymmetrical tonic convulsions with cyanosis, eye deviation, and oral automatism. She was diagnosed with EIMFS based on seizure symptoms and migrating foci on ictal EEG. The seizures were refractory to conventional antiepileptic drugs. Whole-exome sequencing revealed a *de*

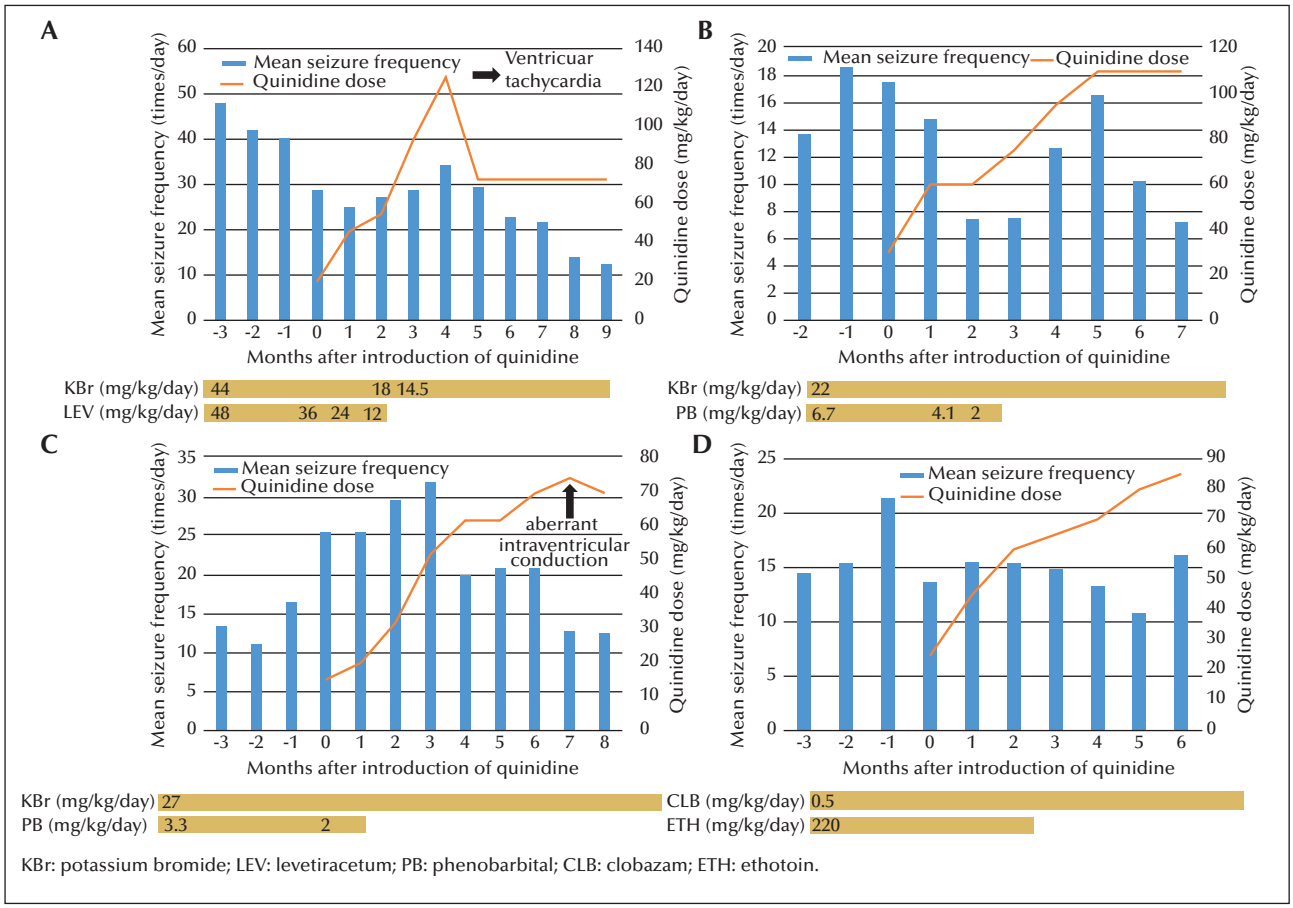

Figure 1. Evolution of seizure frequency: (A) Patient 1; (B) Patient 2; (C) Patient 3; (D) Patient 4.

novo heterozygous mutation in *KCNT1* (c.2800G>A; p.Ala934Thr).

She was administered quinidine at a starting dose of 2 mg/kg/day. The antiepileptic drugs used in combination with quinidine were phenobarbital (6.7 mg/kg/day) and potassium bromide (22 mg/kg/day). Her seizure frequency decreased by approximately 50% after two to three months of quinidine therapy. Subsequently, her seizure frequency increased despite an increase in the quinidine dose at five months after quinidine initiation. The average seizure frequency during the three months before quinidine initiation was 10.8 times/day, and decreased by 48.1% to 5.6 times/day during the last three months (*figure 1B*). The QTc before quinidine initiation was 343 ms, whereas the longest QTc after the initiation of quinidine therapy was 435 ms. The relationship between serum quinidine concentration and quinidine dose is presented in *figure 2B*. The trough levels of quinidine with phenobarbital were lower than those for quinidine without phenobarbital at a quinidine dose of approximately 60 mg/kg/day. The trough and peak levels of quinidine were inconsistent when administered at a dose of around 100 mg/kg/day in the absence of phenobarbital.

Patient 3

Patient 3 was a 21-month-old male born after 36 weeks of gestation. He developed focal seizures comprising eye deviation, oral automatism, asymmetrical tonic posturing, cyanosis, and eye blinking at two months of age. Ictal EEG showed migrating epileptic focus, which resulted in the diagnosis of EIMFS.

Conventional antiepileptic drugs were ineffective, and the frequency of epileptic seizures gradually increased to 30-40 times a day. Phenobarbital was the only anticonvulsant that demonstrated slight efficacy against the seizures, however, the patient suffered from drowsiness as a side effect. Whole-exome sequencing revealed a *de novo* heterozygous mutation in *KCNT1* (c.862G>A; p.Gly288Ser).

At the age of 14 months, the patient was initiated on treatment with quinidine at a dose of 17 mg/kg/day in combination with potassium bromide (27 mg/kg/day) and phenobarbital (3.3 mg/kg/day).

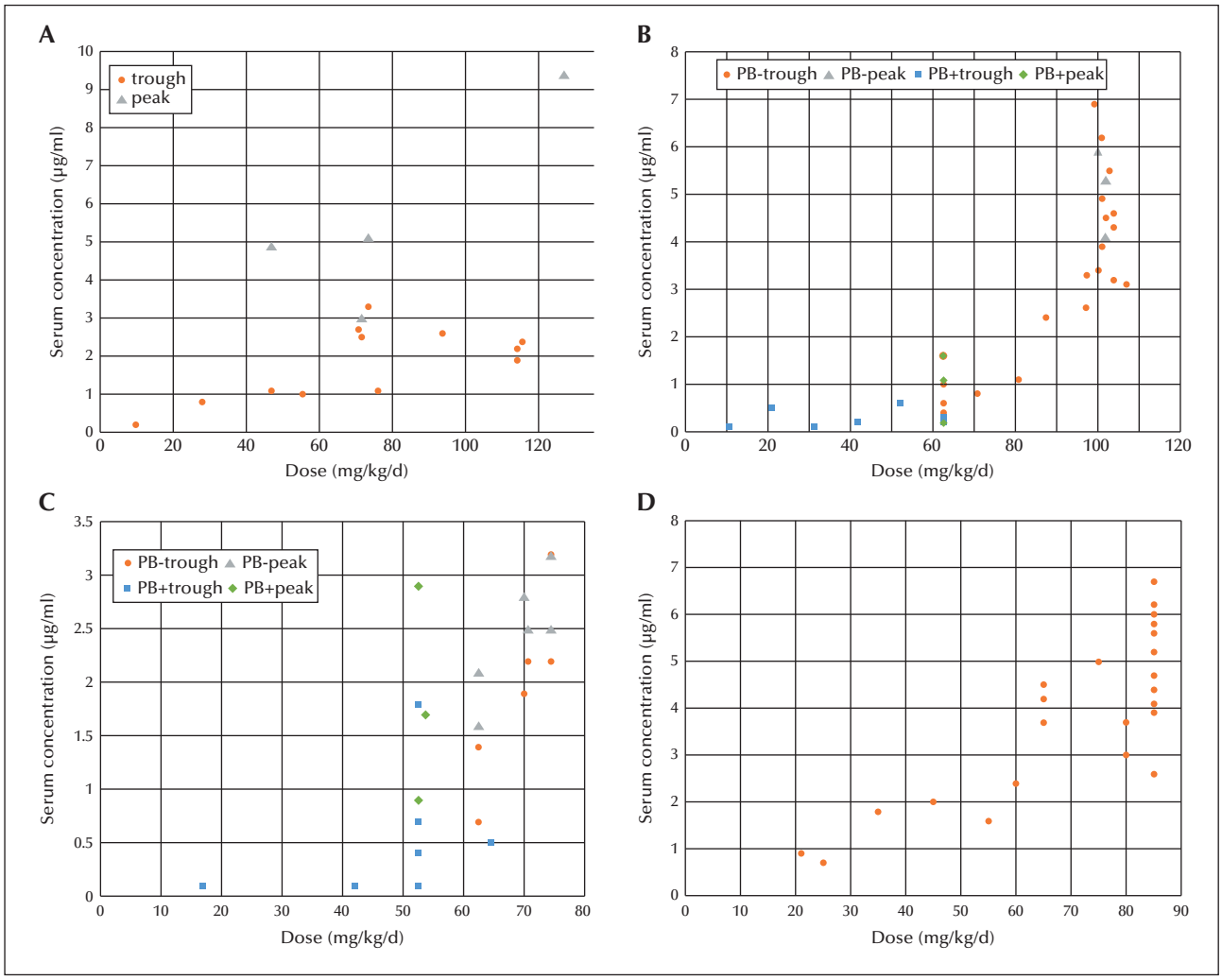

Figure 2. The relationship between serum quinidine concentration and quinidine dose, based on peak and trough levels: (A) Patient 1; (B) Patient 2; (C) Patient 3; (D) Patient 4. PB: phenobarbital.

During the first three months, his seizures worsened despite an increase in the quinidine dose. The average seizure frequency in the three months before quinidine initiation was 14 times/day, and was 12.1% higher at 15.7 times/day during the last three months (*figure 1C*).

The asymptomatic change observed on ECG was noted to comprise a wide QRS, suggesting aberrant intraventricular conduction when the serum trough quinidine concentration was 3.2 μg/ml. Immediately following a reduction in the quinidine dose from 74.5 to 70.7 mg/kg/day, the abnormal ECG findings resolved. The relationship between serum quinidine concentration and quinidine dose is presented in *figure 2C*. Briefly, the trough levels of quinidine at doses less than 50 mg/kg/day remained relatively constant at 0.2 μg/ml despite the increase in dose, which could have been due to a potential effect of phenobarbital. Conversely, the serum quinidine concentrations gradually rose with increases in the quinidine dose to >50 mg/kg/day, in parallel with a reduction in the phenobarbital dose. Serum quinidine concentration was unstable at the quinidine dose of 53 mg/kg/day.

Patient 4

Patient 4 was a nine-year-old male born after 39 weeks of gestation. His focal seizures comprised asymmetrical tonic posturing and eye blinking, which started at the age of one month. The patient's EEG showed a suppression-burst pattern until the age of 20 months, and he was diagnosed with focal epilepsy. Conventional antiepileptic drugs, methyl prednisolone pulse therapy, and the ketogenic diet were ineffective. Whole-exome sequencing revealed a *de novo* heterozygous missense mutation in *KCNT1* (c.1420C>T; p.Arg474Cys).

Quinidine therapy was initiated at a dose of 21 mg/kg/day at seven years of age and was combined with clobazam (0.5 mg/kg/day) and ethotoin (220 mg/kg/day). Although the quinidine dose was increased to 85 mg/kg/day, the average seizure frequency in the three months before quinidine introduction was 17.3 times/day, and was 23.1% lower at 13.3 times/day during the last three months (*figure 1D*). No quinidine-related side effects, such as ECG changes, were observed. The serum quinidine concentrations of the patient are shown in *figure 2D*. Although the trough levels of quinidine were generally associated with quinidine doses <80 mg/kg/day, the serum quinidine concentration was inconsistent at quinidine doses >80 mg/kg/day.

Discussion

Quinidine was effective in only one of the four patients presented herein, based on >50% seizure reduction as the definition of quinidine efficacy. The most effective trough and peak serum quinidine concentrations for Patient 1 were 2.2-3.3 μg/ml and 5.1 μg/ml, respectively. The quinidine levels of Patient 1 were close to the previously reported effective serum quinidine levels for epilepsy that ranged between 0.4 and 5 μg/ml (Bearden *et al*., 2014; Mikati *et al*., 2015; Fukuoka *et al*., 2017; Abdelnour *et al*., 2018). The timing of initiation of treatment in Patient 1, however, was far later than that reported in previous reports (Bearden *et al*., 2014; Mikati *et al*., 2015; Fukuoka *et al*., 2017; Abdelnour *et al*., 2018; Mullen *et al*., 2018). Additionally, seizure frequency often fluctuates during the natural course of EIMFS. Therefore, it is unclear whether the seizure reduction in Patient 1 was indeed due to quinidine.

Seven studies published to date include a total of 15 epilepsy patients treated with quinidine: four patients with EIMFS, 10 with other focal epilepsy, and one with West syndrome (Bearden *et al*., 2014; Mikati *et al*., 2015; Chong *et al*., 2016; Fukuoka *et al*., 2017; Abdelnour *et al*., 2018; Madaan *et al*., 2018; Mullen *et al*., 2018). Among these patients, three of the four patients with EIMFS responded well to quinidine (3/4; 75%). With the inclusion of our three patients with EIMFS, whose statuses improved, quinidine was overall effective in four out of seven patients (4/7; 57.1%). In contrast, no patients with other focal epilepsies, including Patient 4 in the current study, responded to quinidine (0/11; 0%). Quinidine was effective in the only reported patient with West syndrome who was treated with quinidine (1/1; 100%) (Fukuoka *et al*., 2017). Overall, these results suggest quinidine as a promising treatment option for some patients with EIMFS and West syndrome, however, quinidine may not be beneficial for patients with other focal epilepsies.

All *KCNT1* mutations in the current four patients were reported previously (Bearden *et al*., 2014; Mikati *et al*., 2015; Chong *et al*., 2016; Fukuoka *et al*., 2017). The *KCNT1* mutation c.1283G>A (p.Arg428Gly) has been detected in a total of three patients, including Patient 1 in the current study (Bearden *et al*., 2014; Chong *et al*., 2016). Although quinidine was partially effective for Patient 1 in the current study and the patient reported by Bearden *et al*., both of whom had EIMFS, it was not beneficial in patients suffering from focal epilepsy (Chong *et al*., 2016). Although not conclusive, these results based on the available reports and our cases suggest that quinidine therapy should be considered in patients with EIMFS who harbour the *KCNT1* mutation, c.1283G>A (p.Arg428Gly).

A previous study suggested that age of the patients might be an important factor for the efficacy of quinidine therapy (Abdelnour *et al*., 2018). The authors found that all patients who showed good response to quinidine therapy were under the age of four and that no patient over four years of age responded to quinidine. Although the response of Patient 1 in the current report is consistent with their finding, the outcomes of the remaining three patients do not lend support. In another report, a patient with EIMFS who was started on quinidine at six months of age also failed to respond (Madaan *et al*., 2018). Importantly, factors other than age should be considered which could account for the observation of Abelnour *et al*. and the disgreement between their study and ours. In the study by Abdelnour *et al*., the seizure types of the four patients under four years of age corresponded to EIMFS or West syndrome, whereas the seizure types of the four patients over four years of age corresponded to other focal epilepsies (Abdelnour *et al*., 2018). Given that the patients with EIMFS and West syndrome showed a better response to quinidine than those with other focal epilepsies in the study of Abdelnour *et al*. (2018) as well as in the current study, age at the time of quinidine treatment initiation may not be a good prognostic factor. Future studies are warranted to clarify important prognostic factors for good response to quinidine therapy.

Based on previous studies comparing psychomotor development before and after quinidine administration, psychomotor development was reported to improve perceptibly in two patients with EIMFS who achieved complete or partial seizure suppression. A three-year-old male with 80% seizure reduction became more alert and more interactive (Bearden *et al*., 2014), whereas a three-year-old female with complete seizure suppression began to utter words after initiating quinidine therapy (Mikati *et al*., 2015). However, none of the patients in the current study, including those with seizure reduction, showed improvement in their development after initiating

quinidine therapy, and their psychomotor development remains severely delayed.

All patients in the current study were administered quinidine three or four times a day. In this study, trough was defined as the timepoint immediately before the second administration of the day, and peak was defined as the timepoint 2.5 hours after the first administration. The relationship between serum quinidine concentration and quinidine dose was inconsistent among the patients, and increased concentrations were reported even though the dose remained the same.

In the current study, two out of the four patients were administered phenobarbital in combination with quinidine. During the clinical course for these two patients, the elevation in quinidine concentration was significantly hindered due to the induction of cytochrome P450 3A4 by phenobarbital, which metabolises quinidine (*figures 2B, C*). It took several weeks for quinidine concentrations to increase after the discontinuation of phenobarbital, suggesting that the aftereffect of phenobarbital on quinidine concentration lingers. Therefore, careful quinidine titration should be planned when drugs that induce cytochrome P450 3A4 are used in combination with quinidine.

At the time of ventricular tachycardia in Patient 1, the peak serum quinidine concentration with a quinidine dose of 126 mg/kg was 9.4 μg/ml, both of which were higher than previously reported for this patient and the other patients in the current study. Moreover, arrhythmia appeared within one day after the increase in quinidine dose. Several studies have also reported that cardiac arrhythmias generally occur within days of quinidine administration (Cohen *et al*., 1977; Roden *et al*., 1986; Hohnloser *et al*., 1995). These results suggest that careful patient monitoring, particularly after the administration of, and an increase in, the quinidine dose, is critical. Additionally, a previous report described a small number of patients who developed *torsade de pointes* during long-term quinidine therapy, usually in association with hypokalaemia (Roden *et al*., 1986). The serum potassium level of Patient 1 at the onset of arrhythmia was 4.4 mEq/l, which was within normal limits.

QT elongation with quinidine was observed in seven out of the 15 patients reported in the literature (Mikati *et al*., 2015; Fukuoka *et al*., 2017; Abdelnour *et al*., 2018; Mullen *et al*., 2018). Notably, one patient treated with quinidine developed QT elongation despite a low serum quinidine concentration of 0.4 μg/ml (Abdelnour *et al*., 2018) or a low dose of 34.4 mg/kg/day (Mikati *et al*., 2015). Clearly, instances of QT elongation do not translate to an increased risk of arrhythmia or require urgent discontinuation of quinidine, because QT elongation itself only reflects the primary action of quinidine on ion channels. To achieve a truly safe range of serum quinidine level and dose is considerably difficult because its toxic levels depend on genetic factors, electrolytes, and other complications such as serum concentration and dose. However, it remains certain that a quinidine dose over 74.5 mg/kg/day or a serum quinidine concentration above 9.4 μg/ml during treatment can lead to issues that are more serious than QT elongation.

Because quinidine remains one of the few promising therapeutic drugs for patients with EIMFS harbouring *KCNT1* mutations, elucidating optimal serum quinidine concentrations and appropriate methods of titration is essential for its safe and effective use. There is a possibility that serum quinidine levels may not be directly related to efficacy or side effects, which requires additional case reports and case series for clarification.

The current report has several limitations. First, this was a small, open-label study. Additionally, the possibility remains that the seizure reduction observed in our patients after the introduction of quinidine was due to the natural history of the disease, and the true efficacy of quinidine in patients with *KCNT1* mutations remains to be elucidated. Finally, it should be noted that quinidine therapy has not yet been approved in patients with EIMFS and *KCNT1* mutations and should be prescribed with caution due to serious side effects. □

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

Acknowledgements and disclosures.

This study was approved by the Institutional Review Board of the National Epilepsy Center, NHO Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka, Japan. None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) Which epilepsy syndromes are believed to show a response to quinidine therapy?

(2) Which antiepileptic drugs suppress serum quinidine concentration?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".