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Case Report

Quinidine therapy for West syndrome with *KCNT1* mutation: A case report

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Abstract

The *KCNT1* gene encodes the sodium-dependent potassium channel, with quinidine being a partial antagonist of the KCNT1 channel. Gain-of-function *KCNT1* mutations cause early onset epileptic encephalopathies including migrating partial seizures of infancy (MPSI). At 5 months of age, our patient presented with epileptic spasms and hypsarrhythmia by electroencephalogram. Psychomotor retardation was observed from early infancy. The patient was diagnosed with West syndrome. Consequently, various antiepileptic drugs, adrenocorticotropic hormone therapy (twice), and ketogenic diet therapy were tried. However, the epileptic spasms were intractable. Whole exome sequencing identified a *KCNT1* mutation (c.1955G>T; p.G652V). At 2 years and 6 months, the patient had daily epileptic spasms despite valproate and lamotrigine treatment, and was therefore admitted for quinidine therapy. With quinidine therapy, decreased epileptic spasms and decreased epileptiform paroxysmal activity were observed by interictal EEG. Regarding development, babbling, responsiveness, oral feeding and muscle tone were ameliorated. Only transient diarrhea was observed as an adverse effect. Thus, quinidine therapy should be attempted in patients with West syndrome caused by *KCNT1* mutations, as reported for MPSI.

Keywords: Potassium channel; Epileptic spasms; Epileptic encephalopathy; Treatment; Children

1. Introduction

The *KCNT1* gene encodes a sodium-dependent potassium channel. *KCNT1* mutations are reported to cause early onset epileptic encephalopathies (EOEE) including

Abbreviations: EOEE, early onset epileptic encephalopathy; MPSI, migrating partial seizures of infancy; LTG, lamotrigine; VPA, valproate

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migrating partial seizures of infancy (MPSI) and autosomal dominant nocturnal frontal lobe epilepsy [1–3]. To date, only gain-of-function *KCNT1* mutations have been reported. Quinidine, a partial antagonist of the KCNT1 channel (Slack), may be useful in treating *KCNT1*-related epilepsies. Here, we describe a male patient with West syndrome caused by a *KCNT1* mutation, and his treatment approach.

2. Case report

The male patient was born normally at 40 weeks of gestation, with a birth weight of 2990 g. There was no family history of epilepsy. From birth, he exhibited generalized hypotonia. Psychomotor retardation was observed from early infancy. At 5 months of age, epileptic spasms emerged, and hypsarrhythmia was evident on interictal electroencephalogram (EEG). Epileptic spasms occurred with generalized slow waves and superimposed fast activity followed by voltage attenuation. Based on this EEG pattern, the patient was diagnosed with West syndrome. Spasms were occasionally followed by partial seizures that manifested as rhythmic slow waves in the left temporal region. Brain MRI showed no abnormalities. Valproate (VPA), vitamin B6, zonisamide, topiramate, nitrazepam, and lamotrigine (LTG) failed to control the seizures. Adrenocorticotropic hormone therapy at 4 and 9 months of age did not control recurring seizures after 2 and 4 months of treatment, respectively. At 16 months of age, a ketogenic diet was initiated. The seizure frequency decreased but was not totally controlled. The ketogenic diet was discontinued after 3 months because of difficulties with it, and his intractable spasms recurred. Whole exome sequencing identified a novel heterozygous *KCNT1* mutation (NM_020822.2:c.1955G>T, NP_065873.2:p.G652V) that was predicted to be pathological by two of three *in silico* analysis programs [Pathological in SIFT (score 0.00, scores below 0.05 predict intolerant substitutions) and MutationTaster (score 0.999, a value close to 1 indicates a high security of the prediction), but not Polyphen-2 (score 0.167, scores were evaluated as 0.000 (most probably benign) to 1.000 (most probably damaging))] (Fig. 1). The mutation was not found in our 575 control exomes or Exome Variant Server (http://evs.gs.washington.edu/EVS/). Only one of 104,816 alleles was found in ExAC database (http://exac.broadinstitute.org/). The mutation was located in the C-terminal domain where pathological mutations are reported to cluster [4].

At 2 years and 6 months, the patient was admitted for quinidine therapy. At admission, pure epileptic spasms occurred 60–80 times a day despite treatment with VPA (dosage: 40 mg/kg/d, concentration: 67.9 μg/ml) and LTG (dosage: 3 mg/kg/d, concentration: 4.9 μg/ml). Other seizure types were not observed. Interictal EEG showed multifocal irregular spikes and polyspikes (Fig. 2a, b). Ictal EEG was typical of epileptic spasms. Examination showed severe psychomotor retardation with no meaningful words and low muscle tone. After obtaining approval from the institutional ethical committee and informed consent from the family, quinidine therapy (with concomitant VPA and LTG) was started with electrocardiographic (ECG) monitoring. The starting dose was 2 mg/kg per day, and was titrated upwards at a pace of 2 mg/kg daily. When the quinidine dose reached 60 mg/kg per day, serum levels ranged from 2.7 to 4.8 μg/mL (target level: 2.0–6.0 μg/mL). With quinidine therapy, his epileptic spasms decreased to 10–30 times a day. Interictal EEG showed a decrease in epileptiform paroxysmal activity (Fig. 2c, d). Further, his development improved, including babbling, responsiveness, oral feeding, and maintaining a sitting position. With regards adverse events, transient diarrhea occurred but spontaneously resolved. On ECG, the corrected QT (QTc) interval was prolonged from 368 ms before quinidine therapy to 407 ms with a dose of 60 mg/kg/day. Nevertheless, QTc intervals were within the normal limit of 450 ms at both stages, and no arrhythmia was observed. Reduced seizures were maintained for 5 months with quinidine, VPA, and LTG treatment, therefore LTG treatment was tapered and finally discontinued. The seizures did not aggravate after discontinuation of LTG, therefore VPA and quinidine combined therapy was continued.

3. Discussion

In the present case, quinidine therapy was effective in reducing epileptic spasm frequency, improving abnormal EEG activity, and promoting development, albeit gradually. In addition, no serious adverse reactions (such as arrhythmia) were observed, and quinidine therapy was safe to use. The reported efficacy of quinidine therapy has been contradictory. In two case reports of MPSI due to *KCNT1* mutations, quinidine resulted in decreased seizure frequency or freedom from seizures and improved psychomotor development [1,3]. However, a lack of response with no marked change in seizure frequency was reported in an EOEE case with *KCNT1* mutation [5]. Our literature search found no reports on the use of quinidine in EOEE cases with West syndrome. In the present case, the seizure type consisted of epileptic spasms only at the start of quinidine treatment, suggesting that quinidine treatment may have certain effects on controlling epileptic spasms. Quinidine therapy should be attempted in cases of West syndrome with *KCNT1* mutation, as reported for MPSI.

The dose and titration speed used here was based on a previous case that responded to quinidine treatment (3-year-old patient with MPSI) [1]. In that report, the seizures disappeared transiently when the dose was