Specific Therapy Based on the Genotype in a Malignant Form of Long QT3, Carrying the V411M Mutation

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Summary
Congenital long QT syndrome (LQTS) is a cardiac channelopathy that leads to the prolongation of the QT interval. This prolongation can lead to ventricular tachyarrhythmia, syncope, and sudden cardiac death. There are various types of LQTS. Treatment of LQT1 and LQT2 is mainly based on antiadrenergic therapy. LQT3, on the other hand, is a result of a mutation of the SCN5A gene, which encodes the sodium channels. In this type, patients are sensitive to vagal stimuli and episodes tend to occur at rest. Sodium channel blocking compounds, such as ranolazine, mexiletine, and flecainide, have been found to be effective in selective mutations.

In this case report, we report the case of a child with congenital LQT3 (V411M) who presented first with sudden cardiac death and three weeks later with an implantable cardioverter defibrillator storm. Knowing the specific mutation and understanding the mechanism at the molecular level through an in vitro study yielded a clinically meaningful result. The patient’s arrhythmia burden was totally eliminated following successful treatment with flecainide.

Key words: Long QT syndrome, Flecainide, Sudden cardiac death

Long QT syndrome (LQTS) is an inherited cardiac disorder associated with prolonged ventricular repolarization and a propensity for recurrent syncope and sudden cardiac death caused by malignant ventricular arrhythmias.1-3 In genetic studies, several types of congenital LQTS caused by mutations in the genes of the potassium, sodium, and calcium channels or in the membrane adapter have been identified. Beta blockers were found to be most effective in LQT1 and LQT2, which are caused by mutations in voltage-gated potassium channels and for which cardiac events are associated with exercise or stress.4 Patients with LQT3 experience cardiac events predominantly at rest and not during exercise or stress, are poor responders to therapy with beta blockers, and have a rather adverse prognosis.4-8 Accordingly, the management of patients with LQT3 is rather complex and challenging. LQT3 is caused by mutations in the SCN5A gene encoding the alpha subunit of the voltage-gated sodium channel. LQT3 mutations produce a gain of function, most of them impairing fast inactivation so that the decay of current occurs more slowly or not completely, thus leading to QT interval prolongation.5,6 Clinical and experimental investigations suggested that mexiletine shortens the QT interval in some patients with LQT3 by attenuating the increase in the sodium current. However, in other patients with LQT3, the effect of the drug is much less pronounced and protection from life-threatening arrhythmias is not afforded despite compliance with mexiletine treatment.9 Small clinical trials showed QT shortening with flecainide in patients with LQT3.10,11 It has been shown in in vitro studies that flecainide has a high affinity for the sodium channel protein and provides almost complete correction of the impaired inactivation associated with the KPQ deletion mutation.12 However, flecainide demonstrated a proarrhythmic effect in patients with organic heart disease,13 and provocation of ventricular arrhythmia with flecainide in patients with LQT3 is a distinct possibility. Flecainide has potential to cause ventricular arrhythmias in patients with Brugada syndrome, a genetic disorder also involving mutations in the SCN5A gene.14 This highlights the importance of evaluating the safety and efficacy of flecainide for specific mutations.

Here, we report the case of a child with congenital LQT3 (V411M) who presented first with sudden cardiac death and three weeks later with an implantable cardioverter defibrillator (ICD) storm despite optimal therapy with beta blockers. Identification of the specific mutation and elucidation of the mechanism at the molecular level via an in vitro study yielded a clinically meaningful result. The patient’s arrhythmia burden was totally eliminated following successful treatment with flecainide.
Case Report

A nine-year-old girl, with no known health problems, collapsed suddenly in the bathroom and was admitted to our institution after successful cardiac resuscitation with several successive defibrillation shocks for polymorphic ventricular tachycardia. Her medical history revealed mild dizziness without loss of consciousness three months earlier. She had no family history of sudden cardiac death. Her past history was not significant for any medications or illicit drugs. Physical examination was normal. On admission, her laboratory findings showed hypokalemia (potassium: 2.5 mmol/dL) and anemia (hemoglobin: 10.6 g/dL). Other laboratory data, such as creatinine and magnesium, were in the normal range. The patient received potassium and magnesium. Figure 1 shows an electrocardiogram (ECG) after her potassium level was corrected.

Echocardiography showed no structural heart disease. In the following days of hospitalization a prolonged QT interval up to 640 ms at basal ECG was observed. A 12-lead Holter ECG, which was performed one week after admission, showed a very prolonged QT interval with a QTC between 580 and 670 ms (mean: 610 ms). Both of her parents and her nine older siblings had normal ECG and normal QT interval. She was diagnosed with LQTS and was started on beta blocker (propranolol) treatment. Despite the treatment with potassium, magnesium, and propranolol (2 mg/kg), recurrence of polymorphic ventricular tachycardia treated with DC shock was documented. The circadian rhythm was not demonstrated in these arrhythmic events. The patient was implanted with an ICD, which was programmed to the VF zone (> 222 bpm). No arrhythmia recurrences were observed by the third week of hospitalization, and the patient was discharged home with propranolol 2 mg/dL. After obtaining informed consent, a peripheral blood sample was collected from the patient for molecular testing of KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 genes. Three weeks after discharge, the patient was readmitted because of 10 DC shocks delivered from the ICD. Interrogation of the ICD revealed 14 events of ventricular fibrillation, 10 treated successfully with a DC shock and 4 resolved spontaneously. In addition, 200 events of nonsustained polymorphic ventricular tachycardia were recorded. Figure 2 shows one of the events treated with a DC shock. The ICD parameters were normal. Genetic testing revealed a missense mutation in the SCN5A gene, located in domain I/S6 of the channel, predicting the substitution of valine at position 411 with methionine (V411M). This mutation was reported in several patients with LQTS and was not found in 2,500 healthy controls. Neither of the patient’s parents carried this variant, consistent with a de novo mutation in the proband. Horne, et al. characterized the functional and biophysical properties of the V411M
mutation. They detected a hyperpolarizing shift in the steady-state activation relationship and reactivation of the sodium channel toward a higher open probability during repolarization of the cardiac action potential. Exposure of V411M channels to flecainide, which interacts with the channel in the open state, resulted in a significantly increased block in the mutant channel, as compared with the actions of lidocaine and mexiletine. Based on the above evidence, the dose of propranolol was reduced to 1 mg/kg and orally administered flecainide was started. The patient was monitored and the dose of flecainide was gradually increased from 50 mg to 100 mg b.i.d. Within three to five days after the initiation of flecainide, we noticed a dramatic improvement. Repeat Holter monitoring showed complete disappearance of the ventricular arrhythmia. The patient was discharged on flecainide 100 mg b.i.d. and propranolol 1 mg/kg. At the first follow-up in the clinic two months after the discharge, she was well and no arrhythmia was recorded on her ICD or on Holter monitoring. One month later, the patient ran out of flecainide and the therapy was stopped. She continued the propranolol as usual. Three days after stopping the flecainide, she was admitted with another VF storm. Interrogation of the device revealed 10 events of VF: 3 treated with a DC shock and 7 resolved spontaneously. Flecainide therapy was immediately resumed and no ventricular arrhythmia was recorded. She did not receive any more shocks, and no significant arrhythmia was recorded on the device or on Holter monitoring during the three years of intensive follow-up in the clinic. Figure 3 displays QT interval shortening a couple of months after resuming the flecainide therapy.

Discussion

A review of the medical literature revealed a few patients with LQTS from different ethnic groups, carrying the V411M mutation in the SCN5A gene. Horne, et al. reported a newborn with a very long corrected QT interval, QTC up to 640 ms, with periods of 2:1 atrioventricular block. Therapy with lidocaine or mexiletine did not result in any significant change in the QT interval. The same group, which functionally characterizes the biophysical properties of the LQT3 variant V411M, suggests a novel mechanism for LQT3, a result of a hyperpolarizing shift in the steady-state activation relationship and reactivation of the sodium channel toward a higher open probability during repolarization of the cardiac action potential, coupled with unchanged inactivation compared to the wild type. Lidocaine and mexiletine have been shown to preferentially interact with the inactivated state, whereas flecainide appears to interact with channels in the open state. Owing to the gain-of-function activity of V411M, sodium channels are more susceptible to open-state block by drugs like flecainide. The benefits of flecainide in abbreviating the QT interval were also mentioned in another study by Windle, et al. They studied patients with an SCN5A-DKPQ mutation and showed that the QT interval was significantly shortened even at low heart rates. However, they also underlined the notion that the shortening of the QT interval and normalization of repolarization may not have an antiarrhythmic effect. Additionally, the effectiveness of flecainide in reducing the number of ventricular tachycardias
in patients with SCN5A mutations (R1623Q, G1790D, and Y1795C) was also reported in prior case reports. However, to the best of our knowledge, LQT3 carrying the V411M mutation was reported in the Spanish literature. Recurrence of the ventricular arrhythmia three days after stopping flecainide therapy emphasizes the significant role of flecainide in eliminating the life-threatening arrhythmia in our patient who was carrying the V411M mutation. The effectiveness of flecainide in shortening the QT interval in a two-year-old girl with the V411M mutation. The effectiveness of flecainide in eliminating life-threatening arrhythmia in our patient who was carrying the V411M mutation.

Disclosures

Conflicts of interest: None.

References