Mexiteline Shortened QT Interval and Reduced Ventricular Arrhythmias in a Pedigree of Type 2 Long QT Syndrome Combined with Left Ventricular Non-Compaction

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Summary

In this study, we present a case of a 22-year-old female with a family history of syncope, suffering from recurrent syncpe since childhood. She had an obvious prolonged QTc interval of up to 651 ms, a bifid T wave pattern on electrocardiogram, and torsade de pointes, corresponding to a syncope episode. Additionally, her echocardiogram showed left ventricular non-compaction in the apex. After treatment with mexiletine, the QTc interval has been observed to shorten immediately, and the T wave morphology recovered. A similar effect was also observed in her mother and young sister. Administration of propranolol prolonged her QTc interval. Target sequencing of candidate genes revealed a missense mutation in the pore area of the hERG protein, coded by KCNH2. We diagnosed this as a case of type 2 long QT syndrome in which mexiletine could be effective in shortening the QTc interval.

Key words: Ion channel, Syncope, KCNH2, Sudden death, Therapy

Congenital long QT syndrome (LQTS) has been defined as a hereditary cardiac disease characterized by a prolonged QT interval at basal electrocardiogram (ECG) and a high risk of life-threatening arrhythmia.1) The genetic basis of this disease has been found to be associated with mutations in genes coding for cardiac ion channel subunits or proteins involved in modulating ionic currents.1) Approximately 75% of patients with LQTS have mutations in one of the three major LQTS genes as follows: KCNQ1-encoded IKs potassium channel (LQT1), KCNH2-encoded IKr potassium channel (LQT2), and SCN5A-encoded INa sodium channel (LQT3).2) The use of β-blockers is a cornerstone therapy for LQT1 and LQT2, while the sodium channel inhibitor mexiletine has been found effective for LQT3 patients, as recommended by the guidelines.3) Previous clinical studies have revealed that mexiletine might also help shorten the QTc interval in LQT2 patients.4) Here, we report a case of LQT2 family in which mexiletine shortened the QTc interval and reduced ventricular arrhythmia burden, while a β-blocker prolonged its interval.

Case Report

A 22-year-old female with a history of syncopal episodes since the age of 8 visited our hospital for further evaluation. She reportedly experienced syncope twice to thrice per month while she was sleeping, hungry, and in her perimenstrual period. She was initially diagnosed with epilepsy, despite normal results on her electroencephalograms. She took antiepileptic drugs (magnesium valproate and levetiracetam) as prescribed, but the syncope constantly appeared as before. She also had a remarkable family history of syncope (Figure 1A). Her mother (Figure 1A, II-3) and younger sister (Figure 1A, III-3) reportedly suffer from syncope since adolescence and childhood. Her mother was in her 40s and had suffered syncope eight times, while her younger sister, a 14-year-old girl, experienced the symptoms and received the same antiepileptic therapy with the proband. A craniocerebral operation was planned for the proband as exploratory surgery, and preoperative ECG showed a bifid T wave and a significantly prolonged QTc interval (651 ms) (Figure 2A). Torsade de pointes (TdP) was also recorded in a Holter ECG monitor (Figure 2B).

Her physical and neurological examinations were normal. Serum potassium, monitored several times, ranged between 4.0 and 4.5 mmol/L. Serum magnesium (0.83 mmol/L) and calcium (2.3 mmol/L) were within the normal range. ECG at rest showed a bifid T wave and a pro-
longed QTc interval. Transthoracic echocardiography revealed significant non-compaction of the myocardium in the apex with a non-compaction/compaction ratio of up to 2.4 (NC/C: 17/7 mm) in diastole, which reached the diagnostic criteria of the left ventricular non-compaction (LVNC). This finding was also determined in her mother (NC/C: 17/8 mm), but not in her younger sister (Figure 2D). Since her syncopal attacks were mostly triggered during sleep, we suspected LQT3, but the echocardiographic characteristics suggested LQT2. Her resting heart rate was around 45-55 bpm, which could be further slowed down by β-blockers and could result in a far more prolonged QTc interval. Therefore, we first started mexiletine therapy accompanied by the infusion of KCl (1.5 g/day) and MgSO4 (2.5 g/day). Meanwhile, we performed a genetic evaluation of the proband, the proband’s younger sister, and their mother. Mexiletine at 450 mg/day for 5 days was noted to have shortened the QTc interval on ECG (monitored every day) from 651 ms to 600 ms, and the T wave morphology recovered. Similar results were observed in her sister and mother (Figure 3). The three patients took an exercise stress test, and none of them had ventricular arrhythmias, either ventricular premature or VT, and no prolonged QTc was noted during exercise.

Commercial genetic testing was performed, and whole exons, as well as flanking regions of 89 extended disease-specific genes, were sequenced (Supplemental Text). Genetic testing revealed a KCNH2 missense mutation (c.818 C>T, p.T273M; NM_001204798) (Figure 1B) located in the pore area of the hERG channel (Figure 1C). The mutation was validated via Sanger test in the proband, her mother, and her younger sister. No causative mutations were detected in any other arrhythmia-related or cardiomyopathy-related genes. From all these clinical and genetic findings, we diagnosed her as a case of LQT2 combined with LVNC.

Since the proband had obvious bradycardia and was classified as extremely high risk, an implantable cardioverter-defibrillator (ICD) was advised. After ICD implantation, propranolol (15 mg/day) was added to her prescription, and the intravenous infusion of KCl and MgSO4 was switched to oral Panangin (potassium aspar-
MEXILETINE SHORTENED QTC INTERVAL IN AN LQT2 CASE

Figure 2. A: QTc interval changes of the proband at baseline, after addition of mexiletine and after addition of propranolol. B: Recorded TdP in the proband, corresponding to syncope. C: Recorded TdP and a sinus pause of 4008 ms of TdP in the proband’s sister. D: Left ventricular non-compaction on echocardiogram of the proband (right) and her mother (left).

tate 140 mg and magnesium aspartate 158 mg per tablet, 6 tablets/day). Her QTc interval was a little longer after the addition of propranolol (Figure 2A), and ventricular arrhythmia was not induced during the exercise stress test. In over 1-year of follow-up, the proband complained of four shocks during sleep or rest. The ICD programming showed appropriated shocks for ventricular fibrillation. The echocardiogram showed no progress in the LVNC. The dosage of mexiletine was increased to 600 mg/day thereafter, and a strict follow-up process was continued. The proband showed no symptoms for about 3 months after the dose increment (Supplemental Table).

The proband’s younger sister did not receive an ICD implant due to financial problems. After the addition of propranolol, non-sustained ventricular tachycardia was recorded on the ECG monitor, so we withdrew propranolol and continued with mexiletine 450 mg/day and Panangin. She came to us again 45 days after the initial therapy with seven episodes of syncope and TdP recorded on the Holter ECG monitor. We increased her mexiletine dosage to 600 mg/day and continued the follow-up. She still experienced syncope every 1 or 2 months, especially when she missed a dose occasionally. We emphasized the importance of strict prescription and changed the frequency of mexiletine from 200 mg tid to 150 mg qid. After that, she remained symptomless for about 3 months (Supplemental Table). Their mother has remained symptomless on mexiletine (450 mg/day) and propranolol (15 mg/day).
Figure 3. QTc intervals were shortened after the administration of mexiletine 450 mg/day in the proband, her sister, and her mother.

Discussion

Inherited LQTS is considered a rare syndrome, but it accounts for the majority of sudden death cases, especially in the young population. Beta-blockers have been the main treatment for the majority of LQTS patients, but it is common that patients suffer from cardiac events despite receiving the maximum tolerated dosage of their β-blocker. Certain patient genotypes, onset age, length of QTc interval, and the type of trigger are associated with risk stratification.5,6 For LQT2 patients, cardiac events are triggered less frequently by exercise, and a large number of patients experience cardiac events during sleep, rest, or under a slow resting heart rate.3 This makes β-blockers ineffective for LQT2 as opposed to LQT1, whose triggers are adrenergic mediated.5

This family with LQT2 presented with classic bifid T wave and an extremely long QTc interval. The 24-hour Holter monitoring documented TdP when syncope occurred. They carried a missense mutation, KCNH2-T273M, located in the pore helix area of hERG protein. A previous study revealed this is a pathogenetic loss-of-function mutation, which results in reduced expression of hERG protein and significantly low I<sub>K</sub>, amplitude.9 A phenotypic variation has been found to have existed within the family. The proband and her younger sister had a severe phenotype. They had recurrent syncope before the age of 8, but their mother showed the first symptom in her 20s and had been asymptomatic for over 10 years. Besides, the QTc intervals of the two sisters were longer than 600 ms, while that of the mother was around 500 ms, which was much shorter than that of the daughters. In addition, the proband and her mother had LVNC, characterized by a two-layered myocardium consisting of compacted and non-compacted segments, predominant ventricular trabeculation, and intertrabecular recesses.10 On the contrary, these were absent in proband’s younger sister, and her cardiac events occurred mostly during sleep,
without obvious adrenergic stimulation. Based on the above results, the proband and her sister were classified as extremely high risk, while their mother as high risk.11) Their sinus rate was around 45-55 bpm at rest. This decreased the efficiency of the β-blocker since β-blockers are considered as having heart rate-dependent effects on the QT and QTc intervals in LQTS. At slower heart rates, β-blockers can increase the QT and QTc intervals, while at faster rates during exercise, they shorten the intervals,12) which is consistent with what was seen in this family. Treatments other than left cardiac sympathetic denervation or ICD are required to provide additional choices.

Mexiletine, a late sodium channel blocker, has been recommended for LQT3 both in experimental and clinical trials.13) However, evidence supports its use in other types. Bos et al. reported a median QTc reduction of up to 65 ± 45 ms from 547 ms to 470 ms before and after administering mexiletine, respectively, in 12 LQT2 patients. The patients remained cardiac event-free during follow-up.14) A clinical study with a small sample size observed QTc shortening and no proarrhythmic complication with 2 mg/kg mexiletine infusion in 16 LQT1/LQT2 patients.15) Shimizu et al.16) have also reported that mexiletine abbreviated the QT interval and APD90 and totally suppressed spontaneous TdP in a dose-dependent manner in both LQT2 and LQT3 cellular models via administration of d-sotalol and ATXII. Our experience of VT suppression with oral mexiletine in an LQT2 high-risk family strengthens the evidence. Further, more case studies or large-scale clinical trials are needed to explore the broad application of mexiletine for LQT2 patients.

Conclusion

Mexiletine may be utilized to shorten QTc interval and suppress VT in LQT2 patients when a β-blocker has been deemed ineffective. Patients respond differently to the therapy due to a possible presence of phenotypic variation, even when they possess the same mutation.

Disclosure

Conflicts of interest: None.

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Supplemental Files

Supplemental Text
Supplemental Table
Please see supplemental files; https://doi.org/10.1536/ijh.20-518