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PREVENTIVE THERAPIES USING SODIUM CHANNEL BLOCKERS FOR CONGENITAL LONG QT SYNDROME

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ABSTRACT

Preventive therapy for pediatric patients with congenital long QT syndrome (LQTS) without severe cardiac symptoms has not been established. The objective of this study was to clarify the outcomes of pediatric patients with LQTS who were diagnosed without severe cardiac symptoms and who received preventive therapy using sodium channel blockers (SB). This retrospective study included data from seven patients with LQTS who received preventive therapy using SB. The outcomes of those patients and changes of corrected QT intervals (*QTc*) before and after treatment were studied. Three patients received mexiletine alone, and four patients received combination therapy with propranolol and SB. The median follow-up period from the initial treatment to the last follow-up was one year and one month (range: 6 months to 15 years and 6 months). No cardiac events developed after treatment. The *QTc* values after therapy were significantly shorter than those before: median *QTc* 454 (range: 396–475) vs. 485 (range: 470–527) ms, $P < 0.05$.

KEYWORDS: Congenital long QT syndrome, therapy, sodium channel blockers, mexiletine, sports participation.

INTRODUCTION

Congenital long QT syndrome (LQTS) is a genetically heterogeneous group of heritable disorders of myocardial repolarization linked by the shared clinical phenotype of QT prolongation on electrocardiogram, and an increased risk of potentially life-threatening cardiac arrhythmias.[1] Long term uninterrupted beta-blocker therapy is the mainstay of treatment. However, there are many potential side effects.[2] Moreover, beta-blockers lead to negative exercise tolerance and training responses, and limit exercise capacity.[3,4]

Beta-blocker therapy should be the first-line therapy for LQTS types 1–3 barring contraindications, such as active asthma.[5,6] Beta-blockers are recommended in patients with a diagnosis of LQTS who are asymptomatic with *QTc* $\geq$ 470 ms and/or symptomatic with syncope or documented ventricular tachycardia/ventricular fibrillation.[5,6]

Beta-blockers are associated with a significant reduction in cardiac events in LQTS patients. However, syncope, aborted cardiac arrest, and LQTS-related death continue to occur while patients are on prescribed beta-blockers, particularly in those who were symptomatic before starting this therapy.[7] Studies show that sodium channel blockers (SB) are effective for the prevention of cardiac events in patients who were not refractory to beta-blocker therapy.[8-10] Moreover, the usefulness of treatment using SB in LQTS patients with SCN5A mutation (type 3) has been reported.[11,12]

A school-based electrocardiographic screening program has been developed in Japan.[13] A study showed that the screening program may be effective for early diagnosis of LQTS that may allow intervention before symptoms, and that screened patients should have follow-up equivalent to clinically identified patients.[13] However, preventive therapy for patients without severe cardiac symptoms has not been established.

The objective of this study was to clarify the outcomes of pediatric patients with LQTS who were diagnosed without severe cardiac symptoms and who received preventive therapies using SB.

SUBJECTS AND METHODS

The study protocol was approved by our Institutional Ethics Committee. Consent regarding using clinical and laboratory findings in this study was obtained from patients/ guardians.

This retrospective study included data from seven patients with LQTS who were genetically tested for

mutations in KCNQ1, KCNH2, and SCN5A and who accepted preventive therapy using SB before severe cardiac symptoms developed between August 2018 and February 2020. Genetic tests were performed in a commercially available LQTS genetic-testing laboratory (Kazusa DNA Res. Inst). Outcomes of those patients and changes in corrected QT intervals (*QTc*) before and after treatment were studied.

QT intervals were measured manually using the tangent method in leads II and V5 at rest and at the 3- and 4-min recovery point after the treadmill exercise stress test. Subsequently, the *QTc* values were calculated using Bazett's formula.[14] The largest value of the *QTc* at rest was used for the study. Change in *QTc* before and after therapy was the parameter measured as outcome. Schwartz score before therapy was calculated in each patient.[15] A competitive athlete was defined as one who in addition to recreational sports also participates in an organized team or individual sport that requires systematic training and regular competition against others.[16]

Statistical analyses were performed using Stat Flex Version 6 for Windows (Artech Co., Ltd., Osaka, Japan). Sign and Wilcoxon tests were used. $P < 0.05$ was considered statistically significant.

RESULTS

Seven patients (three males and four females) comprised this study (Table 1). The median age at diagnosis of LQTS was 12 years and 9 months (range: 8 years and 2 months–17 years and 2 months) (Table 1). All patients had *QTc* ≥ 470 ms at diagnosis (Table 1).

Table 1: Patient characteristics.

Pt	Gender	Age	*QTc* (ms)	Score
1	Male	15 y 6 m	470	2.0
2	Male	8 y 2 m	518	3.0
3	Female	17 y 2 m	485	3.0
4	Male	12 y 0 m	515	4.0
5	Female	12 y 4 m	527	3.5
6	Female	12 y 9 m	480	5.0
7	Female	15 y 10 m	483	3.0

Pt: patient, Age: age at diagnosis as long QT syndrome, y: years, m: months, QTc: corrected QT interval, Score: Schwartz score.

Six patients (patients 1, 2, 3, 4, 5, and 7) were SCN5A variant, and three patients (patients 1, 3, and 4) were pathogenic variant (Table 2). One patient (patient 5) was KCNQ1 and KCNH2 pathogenic variant (Table 2), with a family history of sudden death under 30 years old. One patient (patient 6) had asthma and an electrocardiogram with long isoelectric segment with normal symmetrical T wave pattern associated with LQTS type 3.

Table 2: Results of genetic tests.

Pt	KCNQ1	KCNH2	SCN5A
1	BE	BE	PA
2	US	NE	US
3	BE	NE	PA
4	NE	BE	PA
5	PA	PA	US
6	NE	NE	NE
7	NE	NE	US

Pt: patient, BE: benign, PA: pathogenic, US: uncertain significance, NE: negative.

Five patients (patients 1, 2, 3, 5, and 6) were diagnosed with LQTS by a school-based electrocardiographic screening program. Two patients (patients 4 and 7) were diagnosed during clinical evaluation for chest pain. One patient (patient 6) had a history of syncope during times of emotional stress. There were no patients with severe cardiac symptoms, such as aborted cardiac arrest, or who had documented ventricular tachycardia/ventricular fibrillation before the treatment.

Four patients (patients 1, 2, 4, and 7) were competitive athletes with participation in basketball or football. Therapy using propranolol (2 mg/kg/day) was refused among these patients because of the negative impact of propranolol on exercise tolerance and capacity. Moreover, beta-blocker therapy was contraindicated in patient 6 because of asthma.

All patients received initial therapy at the median age of 12 years and 9 months (range: 8 years and 2 months–17 years and 4 months). Two patients received propranolol before treatment with SB (Figure 1). All patients received mexiletine (Figure 1). However, two patients (patients 4 and 7) complained of severe gastric pain soon after mexiletine therapy. Therefore, mexiletine was changed to aprindine hydrochloride in those patients (Figure 1). The routes of administration were oral. The median follow-up period from the initial treatment to the last follow-up was one year and one month (range: 6 months–15 years and 6 months). Three patients (patients 1, 3, and 6) received mexiletine alone, and four patients (patients 2, 4, 5, and 7) received combination therapy with propranolol and SB (Figure 1). Two patients (patients 2 and 7) received propranolol therapy in addition to SB treatment because of prolonged *QTc* values after exercise stress test.

Patient 1: Mexiletine (5.7 mg/kg/day)
Patient 2: Mexiletine (6.5 mg/kg/day)
→ Mexiletine (6.5 mg/kg/day) + Propranolol (1.0–1.2 mg/kg/day)
Patient 3: Mexiletine (6.1 mg/kg/day)
Patient 4: Propranolol (0.6 mg/kg/day)
→ Propranolol (0.6 mg/kg/day) + Mexiletine (2.3 mg/kg/day)
→ Propranolol (0.5 mg/kg/day) + Aprindine hydrochloride (0.5 mg/kg/day)
Patient 5: Propranolol (0.6–1.2 mg/kg/day)
→ Propranolol (1.2 mg/kg/day) + Mexiletine (5.5 mg/kg/day)
Patient 6: Mexiletine (3.3 mg/kg/day)
Patient 7: Mexiletine (4.9 mg/kg/day)
→ Aprindine hydrochloride (0.7 mg/kg/day)
→ Aprindine hydrochloride (0.7 mg/kg/day) + Propranolol (0.5 mg/kg/day)

Figure 1: Preventive therapies using sodium channel blockers.

Four patients (patients 1, 2, 4, and 7) were able to participate in their competitive sports, including soccer and basketball, and another three (patients 3, 5, and 6) were able to participate in their recreational sports. No cardiac events, such as sudden death, aborted cardiac arrest, syncope, and arrhythmic events, developed after the treatment. The *QTc* values after therapy were significantly shorter than those before: median *QTc* 454 (range: 396–475) vs. 485 (range: 470–527) ms, $P < 0.05$ (Figure 2).

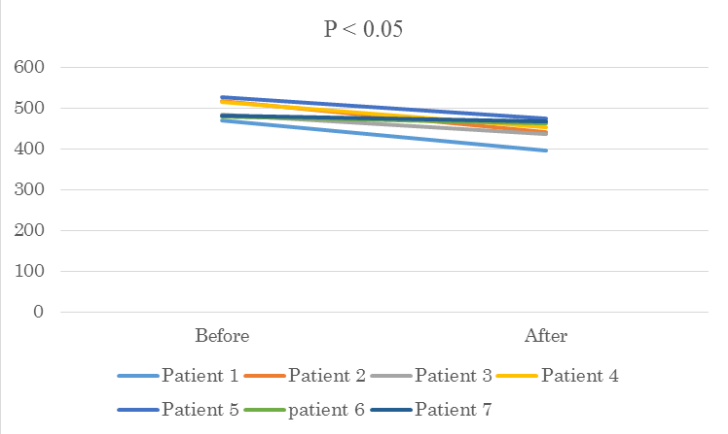
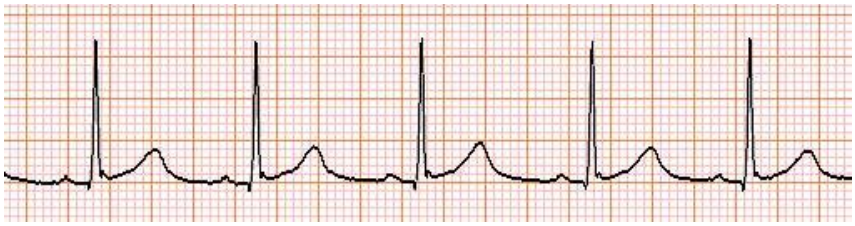
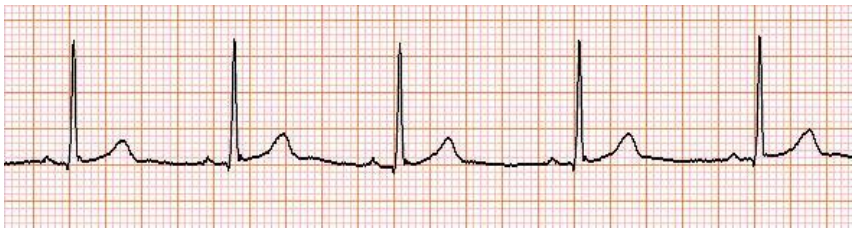


Figure 2: *QTc* changes before and after preventive therapy.

The *QTc* value in patient 1 with LQTS type 3 changed from 470 ms to 396 ms after treatment with mexiletine alone (Figure 3).



Before therapy: *QTc* = 470 ms.



After therapy: *QTc* = 396 ms.

Figure 3: Change of *QTc* before and after therapy in patient 1 lead II electrocardiogram before and after therapy (25 mm/sec).

Adverse effects due to SB were observed in five patients (patients 2, 3, 4, 6, and 7): abdominal pain, including gastric pain in four patients (patient 2, 3, 4, and 7); nausea in two patients (patients 2 and 3); headache in two patients (patients 2 and 6); and transient elevation of aspartate aminotransferase (up to 84 IU/L) and alanine aminotransferase (up to 48 IU/L) values in one patient (patient 4).

DISCUSSION

The main findings of this study were that *QTc* values after preventive therapy using SB were significantly shorter than those before therapy and that no cardiac events, such as sudden death, aborted cardiac arrest, syncope, or life-threatening cardiac arrhythmias, developed after treatment. The *QTc* value is a predictor of the risk of cardiac events in LQTS patients.[1] These findings suggest that preventive therapy using SB may be useful in possible LQTS type 3 patients without severe cardiac symptoms.

A study suggests that beta-adrenergic stimulation induces Torsades de pointes (TdP) by increasing transmural dispersion of repolarization in LQTS type 1 and LQTS type 2, but suppresses TdP by decreasing dispersion in LQTS type 3. Also, beta-blockers are protective in LQTS types 1 and 2, but may facilitate TdP in LQTS type 3.[17] In fact, a case of LQTS type 3 aggravated by beta-blockers and alleviated by mexiletine was reported.[10]

LQTS type 3 is caused by gain-of-function mutations in the SCN5A-encoded Nav 1.5 sodium channel.[18] Cardiac events in LQTS type 3 frequently occur at rest or with inactivity.[18, 19] In comparison with patients with LQTS types 1 and 2, patients with LQTS type 3 have more marked resting bradycardia and incomplete response to beta-blockers. The first cardiac event is more likely to be lethal and seems to occur later in childhood, during or after puberty.[11,18,19] On the basis of these data, and in contrast with the well-established efficacy of beta-blockers in LQTS types 1 and 2, there is anxiety and fear that beta-blockers may not be effective in LQTS type 3 and might, in fact, be proarrhythmic.[10,17,18] This concern has translated into a relatively high use of prophylactic implantable cardioverter defibrillators in LQTS type 3 patients, even among those who are asymptomatic. [18] An international multicenter study showed that beta-blocker therapy reduces life-threatening cardiac events in females with LQTS type 3. The efficacy of beta-blockers for males could not be determined conclusively because of the low number of events.[18] Moreover, three patients (3%) died while on beta-blocker therapy during a median follow-up of > 7 years.[18]

Since arrhythmic events in LQTS type 3 occur predominantly at rest, the value of beta-blocker therapy has been questioned, leaving the management of LQTS type 3 patients uncrtain.[11] Mexiletine is used to block late sodium current and to shorten QT interval in LQTS type 3 patients.[11] A study showed that mexiletine caused a major reduction of life-threatening arrhythmic events besides shortening *QTc* value in LQTS type 3 patients, representing an efficacious therapeutic strategy.[11] The present study showed the shortening of *QTc* value in three patients who received mexiletine monotherapy. Two of those patients (patients 1 and 3) had SCN5A pathogenic mutation and another one patient (patient 6) had T wave characteristic of LQTS type 3. Two patients (patients 2 and 5) with uncertainly significant SCN5 variation received combination therapy with mexiletine and propranolol (Figure 1). *QTc* values shortened after therapy in those patients (patients 2 and 5) (Figure 2). Those findings are consisted with the results mentioned in the previous study that showed the efficacy of mexiletine for LQTS type 3.[11]

Before starting therapy, one of seven individuals (14%) was symptomatic, and six (86%) were asymptomatic in this study. Three of seven patients (43%) had *QTc* values > 500 ms before therapy. No patient experienced arrhythmic events after initiating therapy. A study suggests that the therapeutic goal should not be related to the amount of *QTc* shortening, but rather to obtaining *QTc* values < 500 ms.[11] All patients obtained *QTc* values <500 ms after therapy (Figure 2). The findings in the present study clarified the favorable outcomes of pediatric patients with LQTS who were diagnosed without severe cardiac symptoms and who received preventive therapy using SB.

The successful use of a combination of propranolol and mexiletine to treat isolated cases of malignant perinatal LQTS type 3 caused by the unique SCN5A-G1631D mutations was reported.[20] This study suggests that a combination of mexiletine with propranolol, in the setting of modest tachycardia, is protective of ventricular arrhythmia caused by G1631D.[20] The two patients who received combination therapy with propranolol and mexiletine in the present study (patients 2 and 5) were uncertainly significant SCN5A variant and were not associated with life-threatening arrhythmias before and after treatment. Combination therapy with propranolol and mexiletine was useful for shortening *QTc* in these patients. Combination therapy with propranolol and mexiletine may be useful for pediatric patients with LQTS type 3 who were diagnosed without severe cardiac symptoms.

One study showed the possible effectiveness of aprindine hydrochloride in preventing ventricular tachycardia in patients with LQTS.[8] Another study demonstrated the effectiveness of aprindine hydrochloride in patients with LQTS type 1 who were refractory to beta-blocker therapy.[9] In the present study, aprindine hydrochloride was effective in two patients who had severe gastric pain after mexiletine administration (patients 4 and 7). Aprindine chloride may be useful instead of mexiletine in patients who are not able to continue mexiletine therapy due to its adverse effects.

Patient 5 had KCNQ1 and KCNH2 pathogenic mutations in addition to SCN5A mutation (Table 2). In a model mimicking LQTS type 1 plus 2, the incidence of early after-depolarization was increased compared with that in the LQTS type 1 model under the setting of beta-adrenergic stimulation.[9] Moreover, some LQTS type 1 patients are refractory to beta-blocker therapy and SB may be responsible for the cardiac events.[9]

Although patient 5 had no cardiac events related to LQTS, her *QTc* did not shorten on beta-blocker therapy (527–536 ms). After additional mexiletine therapy, *QTc* shortened from 536 ms to 475 ms (Figure 2). This alleviation is consistent with the finding regarding the usefulness of SB for LQTS in a previous study.[9]

Given the association of cardiac events with exertion or other triggers, prior guidelines for athletes with LQTS were conservative and restrictive.[5] The 2005 Bethesda Conference guidelines recommended that all previously symptomatic LQTS patients or those with electrocardiographic manifestations be restricted to class IA sports, such as billiards, bowling, cricket, curling, golf, and riflery.[5,21] Class IA sports are those with low static (I) and low dynamic (A) stresses according to the classification system outlined by Mitchell et al.[22] The prior rigid recommendations have evolved with the rise of shared decision making and strong supporting evidence to support the liberalization of the former guidelines.[5,6,16,23] The 2015 guidelines stipulated that competitive sports participation except competitive swimming may be considered after institution of treatment for an athlete with either symptomatic LQTS or electrocardiographically manifested LQTS.[23]

A cohort study regarding 26 genotype-positive LQTS patients who participated in competitive sports disclosed that no patient had LQTS symptoms during sports participation.[16] This cohort study included one patient with SCN5A mutation and all 26 patients received beta-blockers. On the other hand, the present study included four LQTS patients with SCN5A mutation, consisting of one patient who received mexiletine alone and three patients who received combination therapy with propranolol and SB. However, no patient had LQTS symptoms during sports participation despite participation in class IC (soccer) and IIC sports (basketball) as defined by Mitchell et al.[22]

Specific triggers cause symptoms in patients with LQTS.[19] LQTS patients with SCN5A mutation (type 3) are most susceptible to events that occur during sleep without arousal (39%), and the prevalence of events due to exercise is 13%.[19] Characteristic triggers in LQTS type 3 patients may be factors regarding the favorable outcomes during sports participation in the present study. The 2005 Bethesda Conference guidelines recommend that the restriction limiting participation to class IA sports may be liberalized for the asymptomatic patient with genetically proven type 3 LQTS.[21] The outcomes of LQTS patients with SCN5A mutation in the present study support this statement.

The limitations of this study include the inclusion of a small number of patients and the retrospective study design.

CONCLUSIONS

The *QTc* values after preventive therapy using SB were significantly shorter than those before. No cardiac event, such as sudden death, syncope, and life-threatening cardiac arrhythmias, developed after treatment. Preventive therapies using SB may be useful in pediatric patients with LQTS type 3 without severe cardiac symptoms.

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CONFLICT OF INTEREST: None.

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