Mid-Term Follow-up of School-Aged Children With Borderline Long QT Interval

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Background: There are no definitive diagnostic criteria or follow-up strategies for long QT syndrome (LQTS) in children with a borderline long QT interval (b-LQT).

Methods and Results: We retrospectively evaluated the clinical course, genetic testing results, corrected QT interval (QTc), and LQTS score of 59 school-aged children (5–18 years old) with a b-LQT (400≤QTc<500 ms). Syncope, but neither aborted cardiac arrest nor sudden cardiac death, occurred in 2 patients during the follow-up (6±3.4 years) with LQTS scores ≥4.5 points. The genetic testing results were positive in 92%, 57%, and 67% of patients with high, intermediate, and low probabilities of LQTS, respectively. The maximum and mean QTc during the follow-up significantly differed among the categories with a probability of LQTS, but not the minimum QTc. However, the QTc at rest and at the recovery point after exercise stress testing dramatically changed at the last follow-up. Consequently, the probability of LQTS changed in half of the patients.

Conclusions: The LQTS score is a reasonable indicator for evaluating school-aged children with a b-LQT, and patients with a low LQTS score appear to be at low risk for cardiac events. However, the LQTS score can change during follow-up. Therefore, when there is doubt or concern for patients with a b-LQT, it is preferable to continue following them. Guidelines on follow-up strategies are desired for b-LQT.

Key Words: Borderline long QT interval; Long QT syndrome; LQTS score; Mid-term follow-up; Schoolchildren

Recently, the probability of a diagnosis of long QT syndrome (LQTS) was reported to be 1:3,298 in children aged 6 years and 1:988 in children aged 12 years based on the ECG school screening program in Japan. Another study reported a high estimated probability of an aborted cardiac arrest (ACA) or sudden cardiac death (SCD) in school-aged children with LQTS, especially in boys with a corrected QT interval (QTc) ≥500 ms. In the international LQTS registry study, the 5-year cumulative probability of ACA or SCD in children and adolescents with a QTc <500 ms with and without a history of syncope was reported to be 11% and 1%, respectively. However, there are no recognized definitions of the upper and lower limits of a normal QT interval. The distribution of the QTc in the normal population and in individuals with LQTS overlaps between 400 and 500 ms. The QTc values of the majority of the general population fall within a range of 400–450 ms, during which LQTS remains possible.

Despite comprehensive genetic testing of the currently known genes, approximately 15–20% of LQTS remains genetically elusive. In a review of channelopathies published in 2013, the considerable problems related to genetic testing were described as follows: “For a patient who presents with a marginal phenotype, a positive genetic test, indicating a genetic variant, may not mean that they have the disease. Worse, there are patients who have a clear clinical phenotype and have a mutation, but the mutation is not linked to the disease. Instead, it may just be a normal variation, conveniently residing as a bystander in the genome of a patient with that phenotype.”
Genetic testing in asymptomatic patients with a borderline LQT interval (b-LQT) seems to have less diagnostic significance than in symptomatic patients. Thus, there are no definitive diagnostic criteria for LQTS in patients with b-LQT, and it is unclear whether follow-up is necessary. However, among children with b-LQT, some have LQTS and are at risk of SCD, and their identification is critical. Therefore, in this study, we retrospectively evaluated the clinical characteristics of school-aged children with a b-LQT (400≤QTc<500 ms) to determine the appropriate follow-up strategy. We assessed the following issues: clinical course during a mid-term follow-up, genetic testing results; and changes in the QTc and LQTS score during the follow-up.

**Methods**

**Patients**
The 122 consecutive pediatric patients were followed from February 1994 to April 2016 because they had prolonged QT interval. The patients who presented only once, and in whom the physician denied the possibility of LQTS and judged no necessity for follow-up, were excluded. The age distribution and reasons for the initial presentation of all patients are shown in Figure 1. We excluded 36 patients aged <5 years from this study, because an exercise tolerance test was unavailable in this age group and they presented at the hospital mainly because of a family history or symptoms. Moreover, 26 patients with a QTc ≥500 ms and who had already received medication were excluded to eliminate any factors unrelated to b-LQT. In total, b-LQT was retrospectively evaluated in 59 patients aged ≥5 years with a QTc ≥400 ms and <500 ms and without medication for a long QT interval.

The authors assert that all procedures related to this work complied with the relevant national guidelines on human experimentation (Japan) and with the Declaration of Helsinki of 1975 (as revised in 2008), and were approved by the institutional ethics committees (Reference no. M28–019).

**Clinical Characteristics**
The following parameters were assessed: sex; age at the initial presentation; reason for the initial presentation; a family history of LQTS; genetic testing results; LQTS score at the initial presentation and at the end of the follow-up; ECG findings at the initial presentation, during the follow-up.

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**Table. Pediatric Patients’ Characteristics According to the Probability of Long QT Syndrome Based on the Long QT Syndrome Score**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>High probability (LQTS score ≥3.5 points)</th>
<th>Intermediate probability (LQTS score 1.5–3 points)</th>
<th>Low probability (LQTS score ≤1 point)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>59</td>
<td>20</td>
<td>29</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Age at the initial presentation (years)</td>
<td>5.3–18 (12.4)</td>
<td>6.2–18.0 (12.6)</td>
<td>6.2–13.4 (12.2)</td>
<td>5.3–13.4 (9.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Reason for the initial presentation (#)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>School screening</td>
<td>48 (81%)</td>
<td>17 (85%)</td>
<td>24 (83%)</td>
<td>7 (70%)</td>
<td></td>
</tr>
<tr>
<td>Family history of LQTS</td>
<td>6 (10%)</td>
<td>1 (5%)</td>
<td>3 (10%)</td>
<td>2 (20%)</td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>5 (8%)</td>
<td>2 (10%)</td>
<td>2 (7%)</td>
<td>1 (10%)</td>
<td></td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>22:37</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of LQTS at the initial presentation (#)</td>
<td>10</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>ECG findings at the initial presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>471±18</td>
<td>465–497 (487)</td>
<td>431–499 (470)</td>
<td>428–459 (451)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Resting heart rate (beats/min)</td>
<td>77±13</td>
<td>72±13</td>
<td>79±12</td>
<td>81±17</td>
<td>NS</td>
</tr>
<tr>
<td>Notched T-wave in 3 leads (#)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up period (years)</td>
<td>6±3.4</td>
<td>6.4±3.1</td>
<td>6.2±3.4</td>
<td>4.8±4.0</td>
<td>NS</td>
</tr>
<tr>
<td>Family history of LQTS at the last follow-up (#)</td>
<td>15</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Medication during follow-up (#)</td>
<td>11</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Follow-up period in the patients without medication (years) (n=48)</td>
<td>6.1±3.6</td>
<td>6.4±3.4</td>
<td>6.2±3.6</td>
<td>5.3±4.5</td>
<td>NS</td>
</tr>
<tr>
<td>No. of resting ECGs during the follow-up in the patients without medication</td>
<td>16±9</td>
<td>16±8</td>
<td>17±9</td>
<td>15±11</td>
<td>NS</td>
</tr>
</tbody>
</table>

LQTS, long QT syndrome; QTc, QT interval corrected using Bazett's formula.12

![Figure 1. Age distribution and reasons for the initial presentation of all pediatric patients with borderline long QT interval. The 36 patients aged <5 years old were presented at the hospital mainly because of a family history (Fx) or symptoms.](image-url)
follow-up, and at the end of the follow-up; findings of the treadmill-based exercise stress test, cardiac events or convulsions before the initial presentation and during the follow-up; and medical treatments for long QT interval. The symptoms that prompted the initial presentation included chest pain, convulsions, and syncope.

The LQTS score was calculated based on the criteria published by Schwartz and Crotti in 2011. A criterion referred to by the original LQTS score was used for a low heart rate according to age (resting heart rate below the second percentile for age). The LQTS score at the initial presentation was retrieved from the data collected during the examination conducted at the initial presentation. At that time, family members who were not diagnosed with LQTS were not counted as LQTS family members. At the end of the follow-up, the QTc and LQTS score were only evaluated in the patients who were followed without any medication for QT prolongation. The latest ECG findings and results of the exercise stress test were used at the end of the follow-up. A history of syncope and family history of LQTS were updated during the follow-up. The categories of the probability of LQTS were the same as those used by Schwartz and Crotti: low probability of LQTS represented ≤1 point, an intermediate probability 1.5–3 points, and a high probability ≥3.5 points.

Measurement of the QT Interval
The QT interval was measured manually using the tangent method in lead V5 or V6 at rest and at the 4-min recovery point after the exercise stress test. Subsequently, the QTc values were calculated using Bazett’s formula. In the case of sinus arrhythmia, the QT interval immediately following the shortest RR interval was used.

School Screening Program for Heart Diseases in Japan
In Japan, there is a nationwide school-based ECG screen-
Schoolchildren With b-LQT

dance of pediatric departments in Japan is 15 years old. In this study, when patients visited hospitals because of the school screening system, the ECGs obtained during the school screening were used as the ones for the initial presentation.

Genetic Testing
Although information on genetic testing was given to all patients, the genetic analysis was only performed in patients who consented. Patients with syncopal episodes, a family history of LQTS, or a QTc at rest $\geq 500$ ms during the follow-up were strongly recommended to undergo genetic testing.

The protocol for the genetic analysis was approved by the institutional ethics committee (Reference no. M24-031-4) and performed under its guidelines. Genomic
DNA was isolated from whole blood using a DNA analyzer (QIAGEN GmbH, Hilden, Germany). Genetic screening for mutations in the KCNQ1, KCNH2, and SCN5A (and, if necessary, KCNE1, KCNE2, and KCNJ2) genes was performed by direct sequencing (ABI 3730 DNA Analyzer; Life Technologies, Carlsbad, CA, USA). The cDNA sequence numbering was based on the GenBank reference sequence. One patient in whom no mutations of KCNQ1, KCNH2, and SCN5A were detected underwent a whole-exon sequencing analysis to identify all the mutations in the known LQTS and candidate genes. The captured DNA was sequenced using the HiSeq™ 2000 (Illumina, San Diego, CA, USA), as described previously. As a result, a rare variant in the cardiac ryanodine receptor gene was detected. We enrolled this patient in the current study, because her ECG had a b-LQT and we followed her as a case of LQTS.

We considered the mutations for which a link with LQTS has already been established in previous publications as disease-causing. In the absence of references, novel variants were included when they were deemed to be pathogenic or likely pathogenic by applying the recently published ACMG guidelines, which are based on criteria using typical types of variant evidence, including the frequencies in the population data and computational (in silico) predictive programs.

**Statistical Analysis**

Data are presented as the mean±standard deviation or median (range) as appropriate, depending on their distribution (Shapiro-Wilk test), using JMP® version 11 software (SAS Institute Inc., Cary, NC, USA). A two-tailed unpaired Student’s t-test or Wilcoxon signed-rank sum test was used to compare the patient characteristics and the QTc among the categories of a probability of LQTS, as appropriate. A two-tailed paired t-test was used to compare the QTc and LQTS score during the follow-up. However, a statistical analysis was not performed to compare the cardiac events during the follow-up and a genetic analysis, because of the small population size.

**Results**

**Clinical Characteristics at the Initial Presentation**

The age at the initial presentations of the 59 patients aged ≥5 years with a QTc ≥400 ms and <500 ms was 12.3 (range: 5.3–18) years (male to female ratio 22:37). The reason for the initial presentation was a school screening in 48 patients (81%), family history of LQTS in 6 (10%), and symptoms in 5 (9%). The symptoms as the reason for the initial presentation included chest pain in 2 patients, syncope in 2, and convulsions in 1. The QTc on the resting ECG was 471±18 ms, and the LQTS score was 3 (range: 0–6.5) points. Based on the LQTS score, a high probability of LQTS (LQTS score ≥4.5 points) was evident in 20 patients (34%), an intermediate probability (1.5–3 points) in 29 (49%), and a low probability (≤1 point) in 10 (17%).

**Clinical Course During the Follow-up**

During the follow-up period (6±3.4 years), no cases of ACA or SCD were observed, but syncope occurred in 2 patients with an LQTS score ≥4.5 points (Figure 2A). Convulsions occurred in 2 patients with an LQTS ≤1 point, but were most likely clinically unrelated to cardiac
arrhythmias.

β-blockers were administered to 11 patients (propranolol in 6 and bisoprolol in 5) after the initial presentation, for syncope in 4 patients, a prolonged QTc in 3, ventricular tachyarrhythmias during the epinephrine loading test or exercise stress test in 3, and convulsions of unknown etiology in one. One patient with a history of syncope and an LQTS score of 3 was not treated, because the syncopal episode was strongly suspected to have a neurologic origin.

Genetic Characteristics

Genetic tests were performed in 31 patients (54%) and the results are shown in Figure 3. Genetic mutations related to LQTS were detected in 11 (92%) of 12 patients with a high probability of LQTS, in 8 (57%) of 14 patients with an intermediate probability of LQTS, and in 4 (67%) of 6 patients with a low probability of LQTS.

Changes in QTc Interval and LQTS Score in 48 Patients Without Medication During the Follow-up

Among the 48 patients not receiving medication, a total of 777 ECGs were evaluated (16 ± 3.0 years; 32 patients who underwent an exercise stress test without medication (time between the initial and last exercise stress tests: 5.9 ± 3.6 years). The maximum and mean QTc during the follow-up significantly differed among the categories with a probability of LQTS, but not the minimum QTc.

The QTc at rest changed dramatically by the last follow-up, albeit, there were no statistical differences (Figure 5A). Regarding the QTc at the 4-min recovery point after the exercise stress test, a dramatic change was also observed in 32 patients who underwent an exercise stress test without medication (time between the initial and last exercise stress tests: 5.9 ± 3.0 years; Figure 5B). Consequently, the LQTS score also changed during the follow-up (Figure 6A). The categories of the probability of LQTS at the last follow-up remained the same as at the initial presentation in 23 of 48 patients without medication (48% of the total). The other 25 (52%) patients, it changed between the initial presentation and last follow-up (Figure 6B).

In females, it changed from a high to an intermediate probability in 2 of 10 patients (20%), and to a low probability in 1 (10%). Among the 16 patients with an intermediate probability of LQTS, it changed to a high probability in 5 (31%), and to a low probability in 8 (50%). In one of 5 patients (20%) with a low probability of LQTS it changed to a high probability and in one to an intermediate probability.

In males, it changed from a high to an intermediate probability in 3 of 4 patients (75%). Among the 10 patients with an intermediate probability of LQTS, it changed to a high probability in 1 patient (10%) and to a low probability in 3 (30%).

Discussion

We examined the clinical characteristics of 59 school-aged children with a b-LQT (400 ≤ QTc < 500 ms) who were suspected of having LQTS. No cases of ACA or SCD were observed, but syncope occurred in 2 patients with a high probability of LQTS during the mid-term follow-up. The genetic test was positive in 92%, 57%, and 67% of the patients with a high, intermediate, and low probability of LQTS, respectively. The maximum and mean QTc during the follow-up significantly differed among the categories with a probability of LQTS, but not the minimum QTc.

The QTc at rest and at the 4-min recovery point after the exercise stress test dramatically changed between the initial presentation and the last follow-up. Consequently, the categories of the probability of LQTS changed by the last follow-up in half of the patients who were followed without medication.

Definition and Incidence of b-LQT

The definition of a b-LQT varies greatly among the published studies. In a study by Viskin, the QTc values of a b-LQT were defined as 400–450 ms for males and 400–460 ms for females. In the expert consensus statement of the Heart Rhythm Society, European Heart Rhythm Association, and Asia Pacific Heart Rhythm Society, it was stated that patients with a QTc of 480–499 ms can only be diagnosed when they have a history of syncope. Therefore, according to that statement, a b-LQT corresponds to a QTc of 480–499 ms without unexpected syncope and <480 ms with or without syncope. In a study of an exercise-based algorithm for the prediction of LQTS published in 2011, a b-LQT was defined as a QTc of 440–460 ms in males and 450–479 ms in females. In the nationwide school-based ECG screening program in Japan, a b-LQT is defined as a QTc ≥ 450 ms at a heart rate <75 beats/min, and ≥500 ms at a heart rate ≥75 beats/min.

It is difficult to determine the incidence of b-LQT because there is no agreed upon definition of the condition. However, in a school-based ECG screening program conducted in Kanazawa, Japan, the prevalence of a long QT interval (≥450 ms for boys and ≥460 ms for girls) in 7,961 schoolchildren was 1.1% in boys and 0.5% in girls. Among those 71 children with a long QT interval, 85% had an LQTS score ≥1 point. In another study of the prevalence of a long QT interval as identified by the school-based screening program in Kagoshima, Japan, it was present in 0.2% of 32,982 1st graders (6–7 years old) and 0.3% of 34,572 7th graders.

Patients with a QTc ≥ 500 ms are diagnosed with LQTS in many studies, but the lower range of the QTc for b-LQT remains unclear. In this study, we defined patients with a QTc ≥ 450 ms and < 500 ms as having b-LQT. We included patients with a QTc ≥ 400 ms and < 450 ms who were suspected to have LQTS, because some of them had LQTS genes and some of them a prolonged QTc during the follow-up (Table S1).

Methods of Evaluating b-LQT

To date, there are 3 main methods of evaluating b-LQT: exercise stress test, epinephrine test, and LQTS score. Among these, the LQTS score appears to be more useful and better suited for use in clinical situations, because it incorporates symptoms, family history, and the results from the exercise stress test.

In this study, we evaluated school-aged children with b-LQT based on their LQTS score. During the follow-up period, syncope only occurred in patients with a high probability of LQTS based on the LQTS score. A positive genetic test occurred in 92% of patients with a high probability of LQTS, but in only 57% and 67% of those with an intermediate and low probability of LQTS, respectively. However, in half of the patients, the categorization of the probability of LQTS changed at final follow-up. The LQTS score is a reasonable method to detect LQTS among school-aged children with b-LQT, but we should recognize that it is not the perfect method.
Follow-up Strategy for b-LQT
Our results indicated the arduousness of identifying LQTS from b-LQTS by a 1-point evaluation. As it stands, when there is doubt or concern about patients with b-LQT, it is preferable to continue following them, because the cumulative rate of ACA or SCD is reported to be around 1–2% at 13 years old in children with a QTc <500 ms.1

We propose that follow-up of patients with b-LQT exhibiting an intermediate or high probability of LQTS at the initial presentation and during the follow-up should be continued. Even in patients with a low probability of LQTS we would perform repeated ECGs, because some of them may show a prolonged QT interval during the follow-up.

Study Limitations
First, the sample size was small and the event rate was low. Second, this study retrospectively evaluated patients subject to sample selection bias, that is, the patients with a prolonged QT interval were judged by the physician as worthy of follow-up. We excluded any patients in whom the physician denied the possibility of LQTS and judged no necessity for follow-up. Third, the assessments were performed at various ages and during differing follow-up periods. Nevertheless, this study yielded important findings about school-aged children with b-LQT.

Conclusions
The LQTS score is a reasonable method of evaluating school-aged children with b-LQT, and patients with a low LQTS score appear to be at lower risk of cardiac events. However, the examination of the LQTS score is not perfect, and the LQTS score can change during the follow-up. It is difficult to identify LQTS from b-LQT by a 1-point observation. Therefore, when there is doubt or concern regarding patients with b-LQT, it is preferable to continue following them. Guidelines are needed for follow-up strategies in patients with b-LQT based on prospective studies involving larger numbers of patients.

Conflicts of Interest
None declared.

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Supplementary Files
Supplementary File 1
Table S1. Results of genetic testing, LQTS score, and QTc in 59 pediatric patients with a borderline long QT interval

Please find supplementary file(s):

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