How Should We Treat School-Aged Children With Borderline QT Prolongation?

Seiko Ohno, MD, PhD

Long QT syndrome (LQTS) is an inherited disease characterized by QT prolongation on the electrocardiogram (ECG) and the risk of ventricular arrhythmias, especially torsades de pointes (TdP).\(^1\) LQTS is one of the causes of sudden cardiac death in young people. Therefore, early diagnosis, life modification and treatments, including medication with β-blockers and the implantation of implantable cardioverter defibrillators in severe cases, are indispensable to prevent unexpected sudden cardiac death.

In Japan, a school-based ECG check-up is routine for the first, seventh and tenth grades.\(^2\) If the ECG shows abnormal findings, including QT prolongation, the student has to consult a pediatric cardiologist. After detailed examination for cardiac disease, the student will be diagnosed with LQTS or another disease. The school-based ECG check-up is very helpful to detect asymptomatic LQTS patients and to prevent cardiac events in LQTS patients.

Risk stratification of LQTS has been well discussed for the past 2 decades. Genotype is one of the factors to predict prognosis, and genetic analysis for LQTS is available in developed countries. Nearly 75% of the LQTS patients are identified as having causative mutations in LQTS-related genes, and 90% of the LQTS patients are genotyped to LQT1 to LQT3.\(^3\) The Table summarizes the risks classified by corrected QT interval (QTc), sex and genotype.\(^4\) LQTS patients with longer QTc (≥500 ms) are classified as high or intermediate risk, whereas those with mild QT prolongation (QTc <500 ms) have intermediate or low risk, regardless of sex or genotype.\(^4\) Not only by genotype, gene mutation and sex-specific risk stratifications have been reported.\(^5,6\) In these reports, QTc ≥500 ms was also an independent risk factor.

In pediatric LQTS patients, age and sex are important factors in predicting prognosis, in addition to the QTc.\(^7\) Boys with LQT1 are at high risk, whereas girls with LQT2 frequently experience TdP after puberty.\(^7\) Therefore, repeated ECG recordings and measurement of the QTc are important to predict the prognosis and to prevent the cardiac events in pediatric LQTS patients. However, no study has shown the changes in QTc and prognosis of students with borderline QT prolongation.

In this issue of the Journal, Miyazazki et al\(^8\) evaluated the clinical course, genetic testing results, QTc and LQTS score of 59 school-aged children (median age 12.4 years, range 5–18 years) with borderline long QT interval (b-LQTs).\(^8\) Among 59 children, 48 (81%) were registered from school screening. Only 4 patients had a history of syncope, and none had suffered an aborted cardiac arrest. The patients were classified into 3 groups of LQTS probability according to their QTc scores: high, intermediate and low. They performed a genetic analysis of 31 patients (54%), and mutations were identified in 23: 9 LQT1, 10 LQT2, 2 LQT3, 1 LQT5, and 1 carried an RYR2 mutation. During the follow-up of 6±3.4 years, an additional patient suffered new-onset syncope, but neither aborted cardiac arrest nor sudden death occurred. In 48 patients who were not received β-blocker therapy after their registration, they analyzed the QTc and LQTS score after follow-up, but there was no statistical difference in the change in QTc and LQTS score, even after taking sex and genotype into consideration. The probability of LQTS worsened in 8 patients: 6 patients changed from intermediate to high, 1 from low to high and 1 from low to intermediate. Therefore, they

Table. Risk for Cardiac Event Before the Age of 40

<table>
<thead>
<tr>
<th>QTc ≥500 ms</th>
<th>QTc &lt;500 ms</th>
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<tbody>
<tr>
<td>Male</td>
<td>Female</td>
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<tr>
<td>LQT1</td>
<td>High</td>
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<tr>
<td>LQT2</td>
<td>High</td>
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<td>LQT3</td>
<td>High</td>
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LQT1, long QT syndrome type 1; LQT2, long QT syndrome type 2; LQT3, long QT syndrome type 3. High, high risk (≥50% probability); Intermediate, intermediate risk (30–49%); Low, low-risk (<30%). Modified from Priori SG, et al.\(^4\)
recommended repeated ECG recordings even for the patients with low probability of LQTS.

One of the limitations of this study was that they did not analyze the change in QTc and LQTS score including the age at registration. Patients whose probabilities worsened were registered at a mean age of 10 years, which was lower than that of patients whose probabilities were unchanged or lowered. In young LQTS patients, clinical symptoms and QTc dramatically change with age, therefore, age at registration is an important factor in predicting the clinical course for the coming several years. Although intensive follow-up for b-LQT will prevent unexpected cardiac events, risk stratification of b-LQT that includes age, sex and genotype is indispensable for the effective follow-up.

In the study, they included a patient who carried an RYR2 mutation, who had been previously reported. RYR2 is a major causative gene for catecholaminergic polymorphic ventricular tachycardia (CPVT), and the phenotype of CPVT resembles that of LQT1, but is more severe, with the first event in CPVT often aborted cardiac arrest. Although the patient with the RYR2 mutation showed QT prolongation and her LQTS score was 6.5, frequent PVCs were detected in her exercise stress test, which was not typical of exercise stress tests in LQT1 patients. Diagnosis and treatment of the patients with QT prolongation and RYR2 mutations will be the next focus in the era of next-generation sequencers.

In conclusion, we have not yet confirmed the definite treatment of school-aged patients with b-LQT. For that, follow-up data from increased numbers of patients with b-LQT from all over Japan will be required.

References