Correction of the QT Interval in Children
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Introduction and Genetic Topics of Long QT Syndrome (LQTS)
LQTS is characterized as prolonged ventricular repolarization with a high incidence of sudden cardiac death because of ventricular arrhythmias, such as torsades de pointes or ventricular fibrillation. Recent advances in genetic studies have revealed 12 genetic abnormalities on the locus of the chromosomes in chromosome 3, 4, 7, 11, 12, 17, 20 and 21. These genetic abnormalities result in decreased function of the potassium channels, increased or prolonged function of calcium channels, or increased function of the sodium channels, which are responsible for the prolongation of ventricular repolarization and consequently cause prolongation of the QT interval.

Recently, not only genetic mutations, but also the segment of the genetic mutation has been reported as important for revealing the risk of cardiac events in some types of LQTS. In LQT1, those with transmembrane mutations of KCNQ1 are at a higher risk of cardiac events than those with C-terminal mutations, and in LQT2, those with pore site mutations of KCNH2 are reported to be at a higher arrhythmic risk than those with non-pore site mutations. According to the location of the genetic mutation, the patients with dominant-negative ion current mutations have a longer QTc interval and higher risk of cardiac events than those with haploinsufficiency mutations associated with LQT1. These functional analyses of ion channels may clarify the severity and prognosis of some cases of QTc in the near future.

In addition to QTc prolongation associated with transmembrane mutations in LQT1 and LQT2, patients, the QTcpeak–end (QTcend–QTpeak) interval is also prolonged in these patients (Figure). The QTcpeak–end is thought to reflect the transmural dispersion of the ventricular repolarization, and the longer the QTcpeak–end is, the greater the chance that a possible cardiovascular accident may occur. In LQT1 patients with transmembrane mutations, the QTcpeak–end is prolonged more by sympathetic nerve stimulation than in patients with C-terminal mutations (Figure A), which may explain the high occurrence of cardiovascular events during exercise in patients with transmembrane mutations.

Diagnosis of LQTS
Unlike the recent advances in genetic testing and functional analysis of ion channels, the clinical diagnosis of LQTS is mainly based on resting 12-lead ECG, clinical symptoms and family history. In children, a total LQTS score <4 points has been reported as associated with an absence of cardiac events in the future, if the children have no cardiac events in their past history. In pediatric patients with a history of cardiac events, family history of cardiac events, lower medication compliance, and lower age at diagnosis are significant risk factors for a cardiac event in the future.

It is well known that the corrected QT interval using Bazett’s formula (QTc = QT / RR1/2) is not suitable for use in children whose heart rates are faster than 75 beats/min. Fridericia’s formula (QTc = QT / RR1/3) is more suitable than Bazett’s for correction of the QT interval for lower and also higher heart rates, but it has not become the standard method for the correction of the QT interval. One reason may be that the power calculation (RR1/3) cannot be done with a standard electronic calculator, but requires a computer or functional electronic calculator. Some ECG machines in Japan can calculate both Bazett’s correction and Fridericia’s correction and by using such machines, more data can be made available for the correction of the QT interval in children.

Although the criteria of Schwartz et al using Bazett’s formula have been highly useful, they mention nothing about age, faster heart rates, or neonates, infants and children. QTc measurements using Bazett’s formula have been reported as useful for screening for LQTS in neonates and infants, but those studies did not use Fridericia’s formula, so it is not possible to determine the efficacy of the latter formula in infants.

Prevalence of LQTS in Children
Schwartz et al reported on the prevalence of LQTS in 44,596 neonates by recording their ECGs. The number of patients with QTc >450 ms was 177 infants (0.41%), 28 had a QTc between 451 and 460 ms (0.06%), 14 had a QTc between 461 and 470 ms (0.03%), and 31 had a QTc >470 ms (0.07%). Genetic mutations were found in 12 of the 28 (43%) with a QTc >470 ms and in 4 of the 14 (29%) with a QTc between 461 and 470 ms. The authors concluded that the prevalence of definite LQTS was at least 1:2,534 (0.04%) apparently healthy live births. Another previous report on the prevalence of LQTS stated it was 0.02% in the normal population, and 0.038% in normal children.

In this issue of the Journal, Hazeki et al found a discontinuous distribution of the QTc interval in the upper 0.025 percentile of school children by using Fridericia’s formula. The prevalence of this discontinuous distribution was 4 in

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4,655 subjects (0.086%). The same group reported an identical prevalence using Bazett’s formula in the same subjects. However, their prevalence of LQTS in the normal population was more than in the other reports. They did not perform a genetic study, and they intended to screen for all possible LQTS patients with their cut-off value.

There has been no previous standard cut-off for screening school children using Fridericia’s formula. Hazeki et al. propose a tentative cut-off QTc value of 430 ms for 1st graders, 445 ms for 7th graders, and 440 and 455 ms for 10th graders, respectively. Further investigation with a genetic study and determination of abnormal QTc values using Fridericia’s formula are needed.

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References