Conclusions—There is a significant effect of age and sex on the QTc interval in long-QT syndrome, with a unique pattern per genotype. The age of 12 to 14 years is an important transitional period. In the risk stratification and management of long-QT syndrome patients, clinicians should be aware of these age-, sex-, and genotype-related trends in QTc interval and especially the important role of the onset of puberty. (Circ Arrhythm Electrophysiol. 2017;10:e004645. DOI: 10.1161/CIRCEP.116.004645.)

Key Words: aging • electrocardiography • long-QT syndrome • pediatrics • sex

Original Article

Effect of Age and Sex on the QTc Interval in Children and Adolescents With Type 1 and 2 Long-QT Syndrome

Arja S. Vink, MD, MSc(EBP); Sally-Ann B. Clur, MBBCh, MSc(Med), FCP(SA)Paed, PhD; Ronald B. Geskus, PhD; Andreas C. Blank, MD, PhD; Charlotte C.A. De Kezel, MD; Masao Yoshinaga, MD, PhD; Nynke Hofman, PhD; Arthur A.M. Wilde, MD, PhD; Nico A. Blom, MD, PhD

Background—In congenital long-QT syndrome, age, sex, and genotype have been associated with cardiac events, but their effect on the QTc interval has never been established. We, therefore, aimed to assess the effect of age and sex on the QTc interval in children and adolescents with type 1 (LQT1) and type 2 (LQT2) long-QT syndrome.

Methods and Results—QTc intervals of 12-lead resting electrocardiograms were determined, and trends over time were analyzed using a linear mixed-effects model. The study included 278 patients with a median follow-up of 4 years (interquartile range, 1–9) and a median number of 6 (interquartile range, 2–10) electrocardiograms per patient. Both LQT1 and LQT2 male patients showed QTc interval shortening after the onset of puberty. In LQT2 male patients, this was preceded by a progressive QTc interval prolongation. In LQT1, after the age of 12 years, male patients had a significantly shorter QTc interval than female patients. In LQT2, during the first years of life and from 14 to 26 years, male patients had a significantly shorter QTc interval than female patients. On the contrary, between 5 and 14 years, LQT2 male patients had significantly longer QTc interval than LQT2 female patients.

Conclusions—There is a significant effect of age and sex on the QTc interval in long-QT syndrome, with a unique pattern per genotype. The age of 12 to 14 years is an important transitional period. In the risk stratification and management of long-QT syndrome patients, clinicians should be aware of these age-, sex-, and genotype-related trends in QTc interval and especially the important role of the onset of puberty. (Circ Arrhythm Electrophysiol. 2017;10:e004645. DOI: 10.1161/CIRCEP.116.004645.)

Key Words: aging • electrocardiography • long-QT syndrome • pediatrics • sex

Congenital long-QT syndrome (LQTS) is a heterogeneous group of inheritable cardiac repolarization disorders, with a predisposition to malignant ventricular arrhythmias that can precipitate syncope, sudden cardiac arrest, or sudden cardiac death.1–3 The delayed repolarization results in a prolongation of the QT interval corrected for the heart rate (QTc) on the electrocardiogram (ECG). The most common types of LQTS are type 1 to 3 (LQT1–3), which are a result of mutations in potassium channel genes KCNQ1 (I_{Ks}) and KCNH2 (I_{Kr}) or sodium channel gene SCN5A (I_{Na}), respectively.4,5

The genesis of LQTS-related cardiac events is not only dependent on the degree of QTc interval prolongation. A complex influence of a variety of factors including age, sex, and genotype is described. Children and adolescents constitute an especially important risk group.5 In children, LQT1 male patients have a higher risk and an earlier onset of cardiac events compared with LQT1 female patients,6–8 but no sex-related differences in LQT2 and LQT3 children have been described.6–9 After the onset of puberty, changes occur in the risk for cardiac events, with an increased risk in LQT2 female patients compared with LQT2 male patients, and no sex-related differences in LQT1 and LQT3 patients.5–9 Unfortunately, there are no data on the influences of age, sex, and genotype on the QTc interval other than comparisons of baseline QTc intervals between categorical age groups.7,8,10,11

See Editorial by Miyazaki and Doi

The onset of puberty plays an important role in sex-related differences in the risk for cardiac events especially in LQT1 and LQT2 patients, which is not seen in LQT3 patients. We hypothesize that the onset of puberty also affects sex-related differences in QTc interval. Therefore, our objective was to...
WHAT IS KNOWN
• In long-QT syndrome (LQTS), the degree of QTc interval prolongation, age, sex, and genotype have been associated with cardiac events.
• The onset of puberty plays an important role in sex-related differences in the risk for cardiac events in especially LQT1 and LQT2 patients.

WHAT THE STUDY ADDS
• There is also an effect of age, sex, and genotype on the trend in QTc interval.
• The age of 12 to 14 years is an important transitional period in sex differences.
• LQT2 patients are probably more sensitive to changes in sex hormone concentrations compared to LQT1 patients.

assess sequential QTc interval data from a large cohort of children and adolescents with LQT1 and LQT2, in order to gain insight in the trend of the QTc interval in LQTS.

Methods

Study Population
A multicenter retrospective cohort study was performed including LQT1 and LQT2 patients born after January 1, 1985. LQTS type was defined as a confirmed pathogenic mutation in either KCNQ1 or KCNH2, detected using conventional methods. Consecutive patients from 5 medical centers in The Netherlands were included until June 2015. Patients were excluded if they were double mutation carriers or a known compound heterozygote. The study was approved by the Academic Medical Center Review Board.

Data Collection and Management
Patients characteristics were collected, and all 12-lead resting ECGs were digitalized, blinded, and manually analyzed by one investigator (A.S.V.) using the open-source image-processing program Image J 1.50h (National Institutes of Health). The QT intervals of 3 consecutive complexes and their preceding R-R intervals were measured in a period without a marked sinus arrhythmia. The duration of the QT interval was determined from the beginning of the QRS complex to the end of the T wave using the tangent method and lead II or V1. If the QT interval could not be determined using lead II and V1, one of the remaining leads was preferably used in all ECGs of that individual patient. The QTc interval was calculated with Bazett’s correction formula averaging the 3 consecutive complexes.

Baseline ECGs were excluded from the analysis if they were made during the first month after birth, during hospital admission, or in the presence of QT-prolonging drugs as registered on CredibleMeds, as were ECGs with ventricular pacing or atrial- and ventricular arrhythmias.

Follow-up duration was defined as the period in years from the date of the first ECG until the date of the latest.

Control Population
The trends in QTc interval for LQTS patients were compared with the trends for healthy controls. To gather information on trends in healthy controls, we used 2 different sources. First, we compared the trends in QTc interval for LQTS patients to the normal median values reported in Dutch children17 and adolescents.18 Age- and sex-dependent normal nonserial values were obtained from population-based prospective cohorts and medical students. Details on the exact measurements are described elsewhere,13,14 but in short, the QT interval was measured by the Modular ECG Analysis System,15 and QTc interval was calculated using the Bazett’s correction formula.

Second, we used the original data from a previous study on the cut-off values for QT intervals in Japanese children and adolescents.16 In this study, serial QT and R-R intervals were obtained at the age of 6, 12, and 15 years in 1240 male patients and 1338 female patients. Three consecutive QT and R-R intervals were measured using the tangent method and averaged. The QTc interval was calculated using the Bazett’s correction formula. Further details of this study are described elsewhere.16

Statistical Analysis
All data were manually entered into a SPSS statistics database version 20.0 and analyzed with R version 3.1.3. We considered 4 subgroups: LQT1 male patients, LQT1 female patients, LQT2 male patients, and LQT2 female patients. Characteristics of the study population were presented as frequencies (percentage) for categorical variables, mean (±standard deviation) for continuous variables with an approximately symmetrical distribution, and median (interquartile range) for continuous data with a skewed distribution. Binary data between 2 groups were evaluated using a χ2 test.

We estimated average age trends in QT interval, heart rate (HR), and QTc interval using a linear mixed-effects model. A mixed-effects model takes account of repeated measurements per patient over time; the number and timing of measurements may vary per patient. To avoid selection bias, all patients with at least one ECG were included in the analysis.17 The QTc interval was allowed to vary smoothly by age via restricted cubic splines. Trends were allowed to differ by sex. The onset of puberty was set at 11.5 years in male patients and 10.7 years in female patients.18 We compared changes between birth and onset of puberty, as well as between onset of puberty and 20 years of age. Sampling uncertainty was quantified via 95% confidence intervals and P values. A P value <0.05 was considered to be statistically significant.

A sensitivity analysis for the trend in QTc interval in the presence of constant medication conditions was performed for (1) β-blocker therapy, (2) propranolol treatment, and (3) both QTc-prolonging19 and QTc-shortening therapy. A more detailed description of the mixed-effects model and the sensitivity analysis is provided in the Data Supplement.

The trends in QTc interval for both control populations were differentiated by sex. The Dutch data, published by Rijnbeek et al,13,14 were plotted as absolute median values, and the Japanese data were analyzed using a linear mixed-effects model, with age as a factor.

Results

Population Characteristics
A total of 343 patients were eligible for the study. Sixty-five patients (19%) were excluded either because they had no ECG (n=63) or only one ECG that was made within 28 days after birth (n=2). These 65 patients were generally referred for genetic testing alone, and follow-up was done in another hospital. The resulting cohort comprised 278 patients from 147 families, which were all included in the analysis. These patients had a total of 2367 ECGs, of which 251 ECGs were excluded from analysis, mainly because they were made during hospital admission (61%), leaving a total of 2116 ECGs for analysis.

Baseline clinical characteristics of all 4 groups are shown in Table 1. The median age at presentation for the total cohort was 8 years (interquartile range, 3–14 years), and most patients were diagnosed as a consequence of family screening (80%). Five percent was symptomatic before presentation, but these patients did not differ in baseline QTc interval duration from asymptomatic patients (P=0.997).

Follow-Up
Fifty-four patients had only one ECG (19%). All were referred for genetic testing, and follow-up was done elsewhere.
Vink et al. Effect of Age and Sex on QTc Interval in LQTS

Genetic testing was most often performed in the context of family screening (76%); 4 patients (7%) had a sudden cardiac arrest. One of these patients had a severe postanoxic encephalopathy, and follow-up was discontinued at the request of the parents. There was no difference with regard to the number of probands (22% versus 19%; \( P = 0.77 \)) and the percentage of symptomatic patients at presentation (8% versus 4%; \( P = 0.46 \)) between patients without follow-up and patients with follow-up. Therefore, the patients without follow-up were considered to be a random sample of the total population, and we assumed that data were missing at random.

Follow-up data of the 224 patients is shown in Table 2. Median follow-up duration was 5 years (interquartile range, 2.5–10 years) with a median number of 8 ECGs (interquartile range, 4–12 ECGs) per patient. Eleven patients (5%) had a cardiac event during follow-up. One of these patients (LQT2 female patient) had symptoms both at baseline and during follow-up. Most of the patients (88%) were on \( \beta \)-blocker therapy during follow-up.

Thirty-seven patients had a set of ECGs during the pubertal period: from 8 to 14 years of age (7 LQT1 male patients, 10 LQT1 female patients, 10 LQT2 male patients, and 10 LQT2 female patients). These patients showed no differences in number of probands (8% versus 22%; \( P = 0.09 \)), symptomatology at presentation (5% versus 5%; \( P = 1.00 \)), or symptomatology during follow-up (8% versus 3%; \( P = 0.37 \)) compared with the other follow-up patients. Therefore, this group was considered to be a random sample of the total study population with respect to trends in QTc interval during puberty.

### Age-Related Changes in QTc Interval

Individual and average age-related changes in QTc interval for LQT1 male patients, LQT1 female patients, LQT2 male patients, and LQT2 female patients are shown in the Figure (A through D). The age-related changes in QTc interval were not statistically significantly different between symptomatic and asymptomatic patients for both LQT1 and LQT2 (\( P = 0.52 \) and \( P = 0.15 \), respectively); however, note that the number of symptomatic patients was small. In addition, there was also no statistically different between probands and family members (LQT1 \( P = 0.30 \) and LQT2 \( P = 0.69 \)).

Age-related changes differed by sex in LQT1 patients (\( P = 0.01 \)). In LQT1 male patients, age significantly influenced the QTc interval (\( P = 0.02 \)). From birth to the onset of puberty, the duration of the QTc interval remained unchanged (\( P = 0.57 \)); after the onset of puberty, the QTc interval shortened until the

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=278)</th>
<th>LQT1 Male Patients (n=60)</th>
<th>LQT1 Female Patients (n=70)</th>
<th>LQT2 Male Patients (n=67)</th>
<th>LQT2 Female Patients (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Presentation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family screening (%)</td>
<td>220 (80)</td>
<td>46 (77)</td>
<td>50 (71)</td>
<td>59 (89)</td>
<td>65 (81)</td>
</tr>
<tr>
<td>Syncope (%)</td>
<td>26 (9)</td>
<td>4 (7)</td>
<td>11 (16)</td>
<td>3 (5)</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Near-drowning (%)</td>
<td>3 (1)</td>
<td>2 (3)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>SCA (%)</td>
<td>7 (3)</td>
<td>1 (2)</td>
<td>2 (3)</td>
<td>1 (2)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Incidental (%)*</td>
<td>9 (3)</td>
<td>3 (5)</td>
<td>4 (6)</td>
<td>1 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other (%)†</td>
<td>11 (4)</td>
<td>4 (7)</td>
<td>2 (9)</td>
<td>2 (3)</td>
<td>3 (4)</td>
</tr>
<tr>
<td><strong>Symptomatic before or at presentation‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Near drowning (%)</td>
<td>7 (2)</td>
<td>3 (5)</td>
<td>4 (6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>SCA (%)</td>
<td>7 (3)</td>
<td>1 (2)</td>
<td>2 (3)</td>
<td>1 (2)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Ventricular arrhythmias (%)</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Median age at first event, y (IQR)</strong></td>
<td>11 (6.0–15.0)</td>
<td>11 (10.5–12.5)</td>
<td>7 (6.0–15.0)</td>
<td>0 (0–0)</td>
<td>16.5 (10.0–20.0)</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (%)</td>
<td>74 (28)</td>
<td>11 (19)</td>
<td>22 (33)</td>
<td>16 (25)</td>
<td>24 (33)</td>
</tr>
<tr>
<td>Positive but not malignant (%)</td>
<td>28 (11)</td>
<td>13 (22)</td>
<td>8 (12)</td>
<td>3 (5)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Malignant (%)‡</td>
<td>162 (62)</td>
<td>35 (59)</td>
<td>37 (55)</td>
<td>45 (70)</td>
<td>45 (62)</td>
</tr>
<tr>
<td>Number of families</td>
<td>147</td>
<td>48</td>
<td>52</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>Probands (%)</td>
<td>55 (20)</td>
<td>14 (23)</td>
<td>20 (29)</td>
<td>7 (10)</td>
<td>14 (17)</td>
</tr>
<tr>
<td>Mean QTc, ms (±SD)</td>
<td>451 (±39)</td>
<td>444 (±33)</td>
<td>451 (±38)</td>
<td>453 (±48)</td>
<td>454 (±35)</td>
</tr>
</tbody>
</table>

LQT1 indicates type 1 long-QT syndrome; LQT2, type 2 long-QT syndrome; IQR, interquartile range; QTc, QT interval corrected for heart rate; SCA, sudden cardiac arrest; and SD, standard deviation.

*Incidental means presentation because of preoperative screening or regular health examination.
†Other means presentation during the evaluation of specific symptoms, that is, palpitations, murmur, dyspnea, chest pain, near-syncope, dizziness, or prenatal symptoms.
‡That is, near-drowning, SCA, or documented ventricular arrhythmias.
Effect of Age and Sex on QTc Interval in LQTS

Table 2. Follow-Up

<table>
<thead>
<tr>
<th>New events during follow-up (%)</th>
<th>All Patients (n=224)</th>
<th>LQT1 Male Patients (n=50)</th>
<th>LQT1 Female Patients (n=58)</th>
<th>LQT2 Male Patients (n=52)</th>
<th>LQT2 Female Patients (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Near-drowning</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>SCA</td>
<td>1 (0)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>9 (4)</td>
<td>0 (0)</td>
<td>4 (7)</td>
<td>0 (0)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>β-Blocker therapy (%)</td>
<td>188/213 (88)</td>
<td>43/47 (91)</td>
<td>53/58 (91)</td>
<td>40/48 (83)</td>
<td>52/60 (87)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Device (%)</th>
<th>Pacemaker</th>
<th>ICD</th>
<th>Median age of start of β-blocker therapy, y (IQR)</th>
<th>Median number of ECGs per patient (IQR)</th>
<th>Median follow-up duration per patient, y (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 (1)</td>
<td>12 (5)</td>
<td>8 (5.0–13.0)</td>
<td>8 (4–12)</td>
<td>5 (2.5–10.0)</td>
</tr>
<tr>
<td></td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>7 (4.0–11.5)</td>
<td>6 (4–10)</td>
<td>5 (3.0–7.0)</td>
</tr>
<tr>
<td></td>
<td>0 (0)</td>
<td>3 (5)</td>
<td>8 (3.0–12.0)</td>
<td>8 (5–11)</td>
<td>5 (3.0–9.0)</td>
</tr>
<tr>
<td></td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>9 (7.0–13.0)</td>
<td>8.5 (5–16)</td>
<td>8 (4.0–11.0)</td>
</tr>
<tr>
<td></td>
<td>2 (3)</td>
<td>6 (9)</td>
<td>9 (6.0–14.0)</td>
<td>7 (4–13)</td>
<td>5 (2.0–10.0)</td>
</tr>
</tbody>
</table>

ICD indicates implantable cardioverter-defibrillator; LQT1, type 1 long-QT syndrome; LQT2, type 2 long-QT syndrome; IQR, interquartile range; and SCA, sudden cardiac arrest.

Discussion

The present study is the first to analyze unique data of serial QTc interval measurements in a large cohort of children and adolescents with LQT1 and LQT2 and has 3 major findings.
Figure. Age-related changes in QT interval corrected for heart rate (QTc) in (A) type 1 long-QT syndrome (LQT1) male patients, (B) type 2 long-QT syndrome (LQT2) male patients, (C) LQT1 female patients, (D) LQT2 female patients, (E) LQT1 and controls, and (F) LQT2 and controls. A–D, Dots are individual measurements, and lines are individual trends. Symptomatic patients are shown in red. The 95% confidence intervals (CIs) for the fitted model are shown. E–F, Lines of LQTs male patients and LQTs female patients combined per genotype. Blue lines are LQTS male patients, and pink lines are LQTS female patients. Both Dutch and Japanese control male and female patients are also shown. Gray lines are control male patients, and black lines are control female patients. The 95% CI for the Dutch controls is not shown. The 95% CI for the Japanese controls is too narrow to be visible.
First, both LQT1 and LQT2 male patients show significant QTc interval shortening after the onset of puberty. Second, in LQT2 male patients, this is preceded by a progressive QTc interval prolongation. Third, the age of 12 to 14 years is an important transitional period in which differences between males and females for both genotypes are seen, ages corresponding with the onset of puberty.

Age- and Sex-Related Changes in QTc Interval in LQTS

Previous studies reported age-related changes in QTc interval of both LQTS male and female patients by comparing children to adults. In LQT1 patients, male children showed longer QTc intervals compared with male adults, and conflicting results were described for LQT1 female patients.7,11 Zareba et al7 reported longer QTc intervals in female children compared with female adults, whereas Ozawa et al11 found no age-dependent changes. Our findings in LQT1 male patients are in line with these previous reports and in agreement with the findings of Ozawa et al,11 observing no age-dependent changes in LQT1 female patients.

In LQT2 patients, Zareba et al7 and Ozawa et al11 both showed no age-related changes in male patients and shorter QTc intervals during childhood compared with adulthood in female patients.7,11 This is in contrast to the results in this study, in which LQT2 male patients have shorter QTc intervals after puberty and LQT2 female patients have no significant change in QTc interval during adolescence.

Differences in QTc interval between male and female patients have only been reported in patients from the age older than 13 or 15 years.7,11 In LQT1 patients, female patients had either a longer QTc interval compared with male patients or no sex-related differences.7 In the present study, we also found that LQT1 female patients have a longer QTc interval compared with LQT1 male patients after the age of 12 years. In LQT2 patients, consistent with previous studies,7,10,11 we also demonstrated that after the second decade, the QTc interval in female patients is longer than that in male patients. However, in contrast to observations in previous studies, we did find sex-related differences in LQT2 patients during childhood, showing a significantly shorter QTc interval in male patients than that in female patients during the first years of life and the opposite between 5 and 14 years, ie, a longer QTc interval in male patients than that in female patients.

This discrepancy between our findings and other studies may be explained by the methodology that was used. The previous studies compared median baseline QTc intervals between dichotomous age groups and did not take individual age trends into account. These aspects may have masked age- and sex-related differences in QTc intervals. The same holds for the trend in QTc interval in the Dutch controls. These controls showed shorter QTc intervals compared with that in LQTS patients, but age- and sex-related differences were not seen.

Sex Hormones

Our findings on age- and sex-related changes in QTc intervals for both LQTS and Japanese controls are most likely the result of changes in sex-specific hormones. Both clinical observational and animal studies have shown a QTc interval shortening because of endogenous testosterone and progesterone.20 Endogenous estrogen lengthens the QTc interval in animal models.20 Concentrations of sex hormones in children are influenced by the activity of the hypothalamic–pituitary–gonadal axis. The hypothalamic–pituitary–gonadal axis is active during the (1) midgestational period in the fetus, (2) first months of life, and (3) pubertal period,7 and, therefore, higher concentrations of testosterone and estrogen are found during these periods.

LQT1 patients have an impaired function of \( I_{\text{Ks}} \) channels, whereas LQT2 patients do not.7 Because testosterone induces a dose-dependent shortening of the action potential duration through enhancement of \( I_{\text{Ks}} \) channels,20 one could postulate that the shortening of the QTc interval by testosterone is less pronounced in LQT1 male patients than in LQT2 male patients because the \( I_{\text{Ks}} \) channels may not be able to fully respond to the presence of testosterone. As a consequence, during periods of sudden changes in sex hormone concentrations (ie, the first months of life and the onset of puberty), a marked QTc shortening would be expected in LQT2 male patients in contrast to LQT1 male patients. This may explain our findings in LQT2 male patients, who showed a shorter QTc interval during the first year and a more pronounced QTc shortening after the onset of puberty compared with LQT1 male patients. This hypothesis is strengthened by the fact that male Japanese controls showed a similar pattern to the LQT2 male patients.

Our data on LQTS female patients also indicate a differing sensitivity to changes in sex hormone concentrations between the genotypes studied because an effect of age on the QTc interval was only found in LQT2 female patients and Japanese female controls. Previous studies have shown that there is a significantly increased risk for cardiac events in LQT2 female patients compared with LQT1 female patients during periods of sudden changes in estrogen concentrations such as the postnatal period,22,23 onset of puberty,5–9 puerperium, first 9 months postpartum,24 and in the pre-, peri-, and postmenopausal periods.25 These data support that LQT2 female patients may be more sensitive to changes in estrogen concentrations compared with LQT1 female patients, and this may be the underlying mechanism for our observations on the QTc interval shortening in LQT2 female patients in the first months of life and the prolongation after the onset of puberty.

Cardiac Events

In LQT1 patients, male patients have a higher risk during childhood and an earlier onset of cardiac events than female patients.6–8 Our observations on sex-related differences in QTc interval could not explain this sex difference in cardiac events during childhood based on the length of the QTc interval because this was similar in male and female patients. These study findings are in line with previous studies,7,10,11 and, therefore, it has been suggested that the difference in risk for cardiac events between LQT1 male and female patients is related to the increased physical activity in male patients compared with female patients during childhood. Because LQT1 patients experience malignant ventricular arrhythmias more...
frequently during physical effort, a presumably higher level of physical activity in male patients may contribute to a higher risk for cardiac events. We only measured the QTc intervals on 12-lead resting ECGs and could, therefore, have missed an impaired QTc response to a higher HR during physical effort in LQT1 male patients.

In LQT2 patients, a higher risk for cardiac events is found in LQT2 female patients after the onset of puberty compared with male patients. On the basis of the findings in this study, this could be explained by a longer QTc interval in female patients.

Modulating Factors

We have considered factors that may have influenced our findings on age and sex differences in QTc intervals. First, in this study, a higher HR is observed in children compared with adolescents of both LQT1 and LQT2 patients. The Bazett correction formula has an optimal correction between 60 and 100 beats per minute, and correction at a slower or faster HR gives erroneous results with, respectively, over- and undercorrection. An HR >100 beats per minute was observed from birth to an age of 3 to 4 years in both LQT1 and LQT2 patients. Therefore, QTc intervals calculated with the Bazett correction formula may be underestimated in this specific time period. Sex-related differences in HR were not observed in this study, which is consistent with previous studies. However, showed that female patients have a more steep QT/R-R ratio than male patients. With the assumption that this also applies to children, the use of the Bazett formula may cause a correction-induced difference between sexes.

Second, medication affecting the QTc interval could have influenced the observed trends in QTc interval in our study. We, therefore, performed 3 sensitivity analyses with the assumption that the introduction of these medications only has a short-term effect on the QTc interval. Sensitivity analyses did not change the results with respect to age- and sex-related differences in QTc intervals. However, we were not able to exclude possible effects of changes in the dose of the medication or the influences of specific types of medications on the QTc interval.

Limitations of the Study

Although this is the largest multicenter study to date examining trends in QTc interval in LQT1 and LQT2 children and adolescents, it has the inherent limitation of being a retrospective study. A complete set of ECGs from 0 to 30 years was not available in all patients, and especially after the age of 25 years, there are limited measurements. Missing ECGs are because of differences in the age of presentation, follow-up intervals, loss to follow-up, and sudden cardiac death. However, as long as those that were followed for a period can be seen as representative for the whole population of similar age, our linear mixed-effect model will provide unbiased estimate of the age trends. Our cohort seems to be a representative sample of the general LQT1 and LQT2 child population, because there were no indications that missing data were not at random. Finally, we were unable to investigate the trends in QTc interval for specific mutations.

Conclusions

There is a significant effect of age and sex on the QTc interval in LQTS, with a unique pattern per genotype. The age of 12 to 14 years is an important transitional period. In the risk stratification and management of LQTS patients, clinicians should be aware of these age-, sex-, and genotype-related trends in QTc interval, especially the important role of the onset of puberty. LQT2 patients should be closely monitored during periods of changes in sex hormone concentrations because they are more sensitive to these variations than LQT1 patients.

Acknowledgments

We are indebted to Martijn de Brujin, Priya Chockalingam, and Robert R. Loontjens for providing ECGs and additional clinical information.

Disclosures

None.

References


Effect of Age and Sex on the QTc Interval in Children and Adolescents With Type 1 and 2 Long-QT Syndrome


Circ Arrhythm Electrophysiol. 2017;10:
doi: 10.1161/CIRCEP.116.004645

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2017 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/10/4/e004645

Data Supplement (unedited) at:
http://circep.ahajournals.org/content/suppl/2017/03/29/CIRCEP.116.004645.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Arrhythmia and Electrophysiology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Arrhythmia and Electrophysiology is online at:
http://circep.ahajournals.org/subscriptions/
Supplemental material

This supplemental material has been provided by the authors to give readers additional information about their work.
Supplemental Methods

Statistical analysis

A repeated measurements analysis with a linear mixed-effects model was used to assess age trends in QT-interval, HR and QTc-intervals. Average age trends (‘fixed effects’) were allowed to differ by gender and were modeled via restricted cubic splines. The restricted cubic spline function allows to explore the effect of age without making restrictive assumptions about the shape of the time trends. Knots were placed at five fixed quantiles of the predictor’s distribution as suggested by Stone.¹ Patients in the study population were considered to be a random sample of the total population. Therefore, we allowed the intercept (i.e. value at birth), slope and quadratic term over age to differ per patient, and assumed these parameters to follow a multivariate normal distribution (random effects). Hence, an unstructured 3x3 covariance matrix for the random effects was used. The correlation between the within-individual residuals as found to be negligible. Changes in QTc-interval from birth to onset of puberty were compared testing for a difference in value between the ages of 0 year and 11.5 years for boys, or 0 years and 10.7 years for girls. These median ages for the onset of puberty were chosen based on observations in a Dutch cohort, where onset of puberty was defined as a testis volume of 4 milliliters in boys and a Tanner stage B2 in girls.²

Sensitivity analysis

We performed some sensitivity analyses in order to assess the influence of changes in therapy for (I) β-blocker therapy, (II) specifically propranolol treatment and (III) the combination of both QTc prolonging and QTc shortening therapy. When a patient switched to β-blocker therapy during follow-up, ECGs made in the absence of β-blocker therapy were excluded with the assumption that the introduction of β-blocker therapy only has a short-term effect on the QTc-interval. Propranolol may have a stronger QTc shortening effect compared to other β-blockers³ (Nadolol is not used in the Netherlands). Therefore, in patients that had varying types of β-blocker therapy, ECGs made during propranolol therapy were excluded. A final sensitivity analysis was performed for the presence of QT prolonging drugs as registered on CredibleMeds®⁴ or in the presence of ‘QT shortening’ therapy i.e. mexiletine, potassium suppletion, potassium-sparing diuretics or left cardiac sympathetic denervation. ECGs made in the presence of these specific conditions were excluded from the analysis. The
introduction of these medications were considered to have a short-term effect on the QTc-interval and therefore they were excluded rather than to include them as a covariate in the model.

References


Supplemental Figures

Figure 1. Age-related changes in Heart Rate in (A) LQT1 Males, (B) LQT2 Males, (C) LQT1 Females, (D) LQT2 Females, (E) LQT1 and (F) LQT2.

A-D: Dots are individual measurements and lines are individual trends. Symptomatic patients are shown in red. The 95% confidence intervals for the fitted model are shown. E-F: Lines of males and females combined per genotype. Blue lines are males and pink lines are females.
Supplemental Figures

Figure 2. Age-related changes in QT-interval in (A) LQT1 Males, (B) LQT2 Males, (C) LQT1 Females, (D) LQT2 Females, (E) LQT1 and (F) LQT2.

A-D: Dots are individual measurements and lines are individual trends. Symptomatic patients are shown in red. The 95% confidence intervals for the fitted model are shown. E-F: Lines of males and females combined per genotype. Blue lines are males and pink lines are females.