Autonomic Function and QT Interval During Night-Time Sleep in Infant Long QT Syndrome

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Background: Sudden infant death syndrome mainly occurs during night-time sleep. Approximately 10% of cases are thought to involve infants with long QT syndrome (LQTS). Autonomic function and QT interval in night-time sleep in early infancy in LQTS infants, however, remain controversial.

Methods and Results: Holter electrocardiography was performed in 11 LQTS infants before medication in early infancy, and in 11 age-matched control infants. Control infants were re-evaluated in late infancy. The power spectral density was calculated and parasympathetic activity and sympathovagal balance were obtained. Electrocardiograms of a representative hour during night-time sleep, daytime sleep, and daytime activity, were chosen and QT/RR intervals were manually measured. LQTS infants had significantly lower parasympathetic activity and higher sympathovagal balance during night-time sleep than control infants in early infancy. These autonomic conditions in early infancy were significantly depressed compared with late infancy. Corrected QT interval (QTc) during night-time sleep (490±20 ms) was significantly longer than that in daytime sleep (477±21 ms, P=0.04) or daytime activity (458±18 ms, P=0.003) in LQTS infants, and significantly longer than that during night-time sleep in controls.

Conclusions: A combination of the longest QTc and autonomic imbalance during night-time sleep in early infancy may be responsible for development of life-threatening arrhythmia in LQTS infants. Critical cases should be included in future studies.

Key Words: Autonomic function; QT interval; Sleep; Sudden infant death

Congenital long QT syndrome (LQTS) is a genetic disorder characterized by delayed repolarization and a long QT interval on 12-lead electrocardiography (ECG). The hallmark of LQTS is syncope or sudden death due to torsade de pointes.\(^1,3\) Sudden infant death syndrome (SIDS) is one of the major causes of death in infancy, with the highest prevalence between 2 and 4 months of age.\(^4,6\) and up to 83% of SIDS deaths occur during night-time sleep.\(^7,8\) SIDS is multi-factorial in origin,\(^4,6\) but prolongation of the QT interval in the first week of life is strongly associated with SIDS,\(^9\) and on genetic analysis approximately 10% of SIDS victims carry functionally significant mutations in LQTS genes.\(^10,11\)

The autonomic nervous system plays an important role in the modulation of cardiac electrophysiology and arrhythmogenesis.\(^12\) Autonomic function matures in infancy, especially in early infancy.\(^13,14\) An abnormality in cardiac sympathetic innervation or in its development is thought to be associated with a prolonged QT interval.\(^15\) SIDS is most prevalent during early infancy, and heart rate variability (HRV), one of the most promising quantitative markers of autonomic activity,\(^16\) has been assessed in pre-term and term infants, and in infants who later died of SIDS, during sleep in early infancy.\(^13,14,17,19\) In these studies, the association between autonomic function and QT interval was also examined,\(^18,19\) but many studies were performed only during daytime sleep\(^13,14,18\) or night-time sleep.\(^17,19\)

The aims of the present study were therefore to assess the circadian change in autonomic function using HRV, and to clarify the differences in QT interval between night-time sleep, daytime sleep, and daytime activity in LQTS infants before starting medication, and in age-matched control infants in early infancy. Autonomic function and QT interval were re-evaluated in late infancy in the same control infants to examine autonomic maturation from early to late infancy.

Methods

Participants

The participants consisted of 11 LQTS infants in early infancy (mean age, 11.8±7.5 weeks) before β-blocker
treated and 11 age-matched control infants (Table 1). The control infants were re-evaluated in late infancy (mean age, 39.6±5.6 weeks). The LQTS infants were not assessed in late infancy, because all LQTS infants were taking β-blockers and the dose per day differed between them (Table 2). The study was approved by the Ethics Committee of the National Hospital Organization Kagoshima Medical Center.

**Diagnosis of LQTS in Infancy**
LQTS was diagnosed when infants had a corrected QT interval by Bazett’s formula (QTc) ≥470 ms on resting ECG, and prolonged QTc was sustained during follow-up at 2 or 3 weeks.

**Genetic Testing**
Genetic testing was performed after obtaining written informed consent. In the first genetic testing, screening for LQT1 (KCNQ1), -2 (KCNH2), -3 (SCN5A), -5 (KCNE1), -6 (KCNE2), and -7 (KCNJ2) was performed using polymerase chain reaction and direct DNA sequencing.

When no pathogenic mutations were identified, in the first study, genes related to LQTS and catecholaminergic polymorphic ventricular tachycardia were retrospectively screened using a targeted gene sequencing method with the HaloPlex Target Enrichment System (Agilent Technology, San Diego, CA, USA) and the MiSeq system (Illumina, San Diego, CA, USA). Detected variants were confirmed using Sanger’s method.

**HRV**
Two-channel 24-h Holter ECG monitoring was performed in all infants. HRV was analyzed on a Holter analysis system (SCM-8000, Ver 54-11, Fukuda Denshi, Tokyo, Japan). After manual checks of the QRS configuration, an R wave was inserted at the midpoint of the long period, when non-normal R wave was detected. The number of non-normal R waves was trivial in the present study. In LQTS infants, control infants in early infancy, and control infants in late infancy, the median of the non-normal R waves was 0.5 beats/day (range, 0–54 beats/day), 0.5 beats/day (range, 0–27 beats/day), and 0.5 beats/day (range, 0–9 beats/day), respectively.

**Table 1. Participant Characteristics**

<table>
<thead>
<tr>
<th>No. participants</th>
<th>LQTS</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>11</td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>6/5</td>
<td>5/6</td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39.1±1.0</td>
<td>39.1±1.2</td>
<td>0.56</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2,901±496</td>
<td>2,974±355</td>
<td>0.90</td>
</tr>
</tbody>
</table>

**Early infancy**

| Age (weeks) | 11.8±7.5 | 11.6±3.4 | 0.52 |
| Weight (g)  | 5,414±1,332 | 5,623±729 | 0.85 |

**Late infancy**

| Age (weeks) | – | 39.6±5.6 |
| Weight (g)  | – | 7,915±1,092 |

Data given as mean±SD. LQTS, long QT syndrome.

**Table 2. LQTS Infant Characteristics**

<table>
<thead>
<tr>
<th>ID no</th>
<th>Sex</th>
<th>First ECG†</th>
<th>Maximum QTc (rest)‡</th>
<th>Maximum QTc (Holter)§</th>
<th>Diagnostic events</th>
<th>Genes</th>
<th>Mutations</th>
<th>Medication</th>
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<tr>
<td>1</td>
<td>F</td>
<td>12.4</td>
<td>0.520</td>
<td>12.4</td>
<td>0.520</td>
<td>Family (mother)</td>
<td>KCNQ1</td>
<td>c.502G&gt;A, p.G168R</td>
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<tr>
<td>2</td>
<td>M</td>
<td>4.4</td>
<td>0.458</td>
<td>9.1</td>
<td>0.472</td>
<td>ECG screening</td>
<td>KCNH2</td>
<td>c.3065delT, p.L1022Pfs+35X</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>5.3</td>
<td>0.483</td>
<td>5.3</td>
<td>0.534</td>
<td>ECG screening</td>
<td>KCNQ1</td>
<td>c.563delG, p.R190Gfs+47X</td>
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<td>3.9</td>
<td>0.485</td>
<td>15.9</td>
<td>0.491</td>
<td>Family (father)</td>
<td>KCNH2</td>
<td>c.65T&gt;A, p.F22Y</td>
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<td>M</td>
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<td>7.6</td>
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<td>Family (mother)</td>
<td>KCNH2</td>
<td>c.65T&gt;A, p.F22Y</td>
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<td>6</td>
<td>M</td>
<td>23.6</td>
<td>0.432</td>
<td>30.9</td>
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<td>7</td>
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<tr>
<td>8</td>
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<td>7.3</td>
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<td>KCNQ1</td>
<td>c.1663C&gt;T, p.R555C</td>
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<tr>
<td>9</td>
<td>F</td>
<td>4.6</td>
<td>0.450</td>
<td>10.9</td>
<td>0.510</td>
<td>ECG screening</td>
<td>KCNQ1</td>
<td>c.1663C&gt;T, p.R555C</td>
</tr>
<tr>
<td>10</td>
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<td>4.6</td>
<td>0.456</td>
<td>25.6</td>
<td>0.489</td>
<td>ECG screening</td>
<td>KCNQ1</td>
<td>c.1663C&gt;T, p.R555C</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>8.0</td>
<td>0.486</td>
<td>10.9</td>
<td>0.488</td>
<td>Family (mother)</td>
<td>KCNH2</td>
<td>c.503C&gt;T, p.P168L</td>
</tr>
</tbody>
</table>

†At first visit to hospital or at ECG screening; ‡on resting ECG at outpatient clinic; ††Holter ECG. ECG screening of 1-month-old infants to identify prolonged QT interval between 2010 and 2011; †††ECG screening of 1-month-old infants to identify prolonged QT interval between 2014 and 2016 (Yoshinaga M; unpublished data, 2018). ECG, electrocardiography; LQTS, long QT syndrome; QTc, Bazett’s corrected QT.
Infant LQTS: HRV and QTc During Sleep

Statistical Analysis
Differences in the means were examined using Mann-Whitney U-test or Wilcoxon signed-ranks test. Differences in QTc and heart rate between night-time sleep, daytime sleep, and daytime activity were analyzed using Friedman’s ANOVA and the Dunn-Bonferroni tests. Spearman’s rank test was used to evaluate the correlation coefficients. Statistical analysis was performed using IBM SPSS Statistics 23 (IBM Japan, Tokyo, Japan). A two-tailed P<0.05 was considered statistically significant.

Results

Participant Characteristics
Gestational age, birth weight, and weight in early infancy were not different between the LQTS and control infants (Table 1). Mutations were identified in 6 of 11 LQTS infants (KCNQ1 in 3 and KCNH2 in 3; Table 2). The mutation in LQTS infant 5 was finally determined on targeted gene screening. Diagnostic events were identified in family studies in five infants and ECG screening programs in five, and by chance in one. ECG screening to identify prolonged QT interval in 1-month-old infants was performed from 2010 to 2011 and from 2014 to 2016.

Circadian Changes in Autonomic Activity in Infancy
LQTS infants had a significantly lower Ln(HF) component at 23:00 hours, 02:00 hours, 03:00 hours, and 06:00 hours than age-matched control infants (Figure 2A). Conversely, LQTS infants had a higher Ln(LF)/Ln(HF) ratio than control infants during night-time at 00:00 hours, 02:00 hours, and at 04:00 hours (Figure 2B). The power of the Ln(HF) component in early infancy in both LQTS infants and control infants, however, was significantly lowered from 23:00 to 03:00 hours, from 05:00 to 07:00 hours, and at 11:00, 12:00, and 15:00 hours compared with that in late infancy in control infants. Conversely, the Ln(LF)/Ln(HF) ratio in early infancy was significantly higher than in late infancy at 23:00 hours, 02:00 hours, and 03:00 hours; from 05:00 to 08:00 hours; and at 11:00, 12:00, and 15:00 hours.

With respect to the autonomic activity according to LQTS genotype, there was no difference in Ln(HF) components or in {Ln(LF)/Ln(HF)} ratio at each hour between infants with the LQT1 and LQT2 genotypes.
three periods is listed in Table S1.

At maximum heart rate, QTc in LQTS infants during night-time sleep was significantly longer than that in controls during night-time sleep (Figure 3A). In LQTS infants, QTc during night-time sleep was significantly longer than that during daytime sleep and daytime activity (Figure 3A). In early infancy in controls, QTc during sleep
Infant LQTS: HRV and QTc During Sleep

Night-time sleep, QTc had a significantly negative association with Ln(HF) at the maximum, average, and minimum heart rate, and a significantly positive association with sympathovagal imbalance at the minimum heart rate (Table 4; Figure 4).

Discussion

LQTS infants had significantly lower parasympathetic activity and higher sympathovagal balance during several night-time hours than control infants in early infancy, but autonomic function in both LQTS infants and control infants in early infancy showed significantly decreased parasympathetic and increased sympathovagal conditions compared with that in late infancy in control infants. Under the conditions of this autonomic dysfunction, LQTS infants had significantly longer QTc at maximum heart rate during night-time sleep than during daytime sleep or daytime activity in early infancy.

In studies of infantile autonomic activity, both term and preterm control infants had increased parasympathetic

Figure 3. Bazett’s corrected QT (QTc) at (A) maximum, (B) average, and (C) minimum heart rate in infants according to long QT syndrome (LQTS) status, time of day, and stage of infancy. Data given as mean and SEM.
activity from early infancy to late infancy during daytime sleep\textsuperscript{13,14} or night-time sleep.\textsuperscript{17} In the present study of the circadian changes in autonomic activity, Ln(HF) power was augmented and Ln(LF)/Ln(HF) ratio was decreased throughout the day, and especially during night-time sleep, from early to late infancy in control infants. This indicates that low parasympathetic activity and a high sympathovagal balance are present during night-time sleep in early infancy. The Ln(HF) power during night-time sleep was negatively associated with QTc, when the data of LQTS and control infants were combined. Considering that sympathetic stimulation precipitates ventricular tachyarrhythmias and sudden cardiac death in patients with LQTS,\textsuperscript{12} the presence of autonomic immaturity during night-time sleep in early infancy is thought to be a high risk factor for life-threatening arrhythmias in LQTS infants.

In the 1970s, Schwartz proposed a hypothesis that an abnormality in cardiac sympathetic innervation or in its development was associated with QT prolongation and was associated with the development of SIDS.\textsuperscript{15} This hypothesis prompted many investigators to measure the QT interval during sleep in healthy controls and in patients with disease conditions. Additionally, during rapid eye movement (REM) sleep, conditions of intermittent bursts of sympathetic activity are present on a background of powerful bursts of parasympathetic activity.\textsuperscript{25-27} Many studies involving adults supported these findings. The QT interval during night-time sleep is longer than that during the daytime or in the awake state.\textsuperscript{28,30} and QTc during REM sleep was longer than that during non-REM sleep, if present.\textsuperscript{31,32}

In the pediatric field, however, the effect of sleep on QT interval was contradictory. Haddad et al measured computer-assisted QT interval in daytime sleep 2–3 h after midmorning feed, and reported that QTc in REM sleep was shorter than that during non-REM sleep in control infants,\textsuperscript{33,34} and in infants who had an aborted SIDS episode in early infancy.\textsuperscript{34} Montague et al determined computer-assisted QTc at five random times throughout the 24-h Holter monitoring period and reported that maximum QTc at these five time points was significantly shorter in infants at risk for SIDS than in age- and sex-matched control infants.\textsuperscript{35} Conversely, Franco et al reported that QTc in infants who later died of SIDS was significantly longer than that in age-matched control infants in the REM, non-REM sleep, and total sleep period,\textsuperscript{19} but that QTc was not different between REM and non-REM sleep in these future SIDS victims.\textsuperscript{19} There are some possible explanations for these discrepancies. Computer-assisted averaged ECG configurations, used in some studies,\textsuperscript{33,35} may not be applicable for infants and children because sinus arrhythmia is frequent and beat-to-beat QT/RR

<table>
<thead>
<tr>
<th>Table 4. QTc and HRV in Early Infancy vs. LQTS Status</th>
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<tr>
<td></td>
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<tr>
<td>QTc at maximum HR</td>
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<td>QTc at average HR</td>
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<tr>
<td></td>
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<tr>
<td>QTc at minimum HR</td>
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HF, high frequency; HR, heart rate; HRV, heart rate variability; LF, low frequency. Other abbreviations as in Table 2.

Figure 4. Bazett’s corrected QT (QTc) at average heart rate vs. the natural logarithm of the high-frequency component (Ln(HF)) during night-time sleep according to genotype in long QT syndrome (LQTS) infants and control infants in early infancy.
intervals are largely changeable in these age groups. In the study that used manual QT measurement, one set of three consecutive beats was chosen for REM and non-REM analysis; this might result in loss of QTc during the intermittent burst of sympathetic activity (at maximum heart rate) and at the powerful burst of parasympathetic activity (at minimum heart rate).

In the present study, therefore, three sets of QT/RR intervals were selected and manually measured at the maximum, average, and minimum heart rates during night-time sleep, daytime sleep and in daytime activity. QTc at the maximum heart rate in night-time sleep may correspond to the condition of intermittent bursts of sympathetic activity on a background of parasympathetic activity. At the maximum heart rate, LQTS infants had a significantly longer QTc during night-time sleep than during daytime sleep or daytime activity. In early infancy in the controls, QTc during night-time and daytime sleep was significantly longer than that during daytime activity. This indicates that night-time sleep is associated with a risk for longer QTc in early infancy, especially in LQTS infants.

No infants with SCN5A mutations were included in the present study. In a study of postmortem genetic screening in victims of SIDS, the most prevalent gene was SCN5A. Arnestad et al reported on 19 SIDS victims with pathogenic mutations associated with LQTS in Norway: five, five, and 13 patients had KCNQ1, KCNH2, and SCN5A mutations, respectively. Ogatiri et al reported on four SIDS victims in Japan, consisting of one with KCNQ1, one with KCNH2, two with SCN5A, and one with digenic KCNH2 and SCN5A mutation. Conversely, Horigome et al reported on 58 infants with congenital LQTS in Japan diagnosed in the fetal, neonatal, and infantile periods, including 11 with KCNQ1, 11 with KCNH2, and 6 with SCN5A mutations. They also reported that one patient each from these three genotype groups developed aborted cardiac arrest. This suggests that the most prevalent genotypes of congenital LQTS diagnosed in the infantile period are KCNQ1 and/or KCNH2 when we combine the SIDS victims and the patients diagnosed in the infantile period. No data that can explain the absence of patients with SCN5A mutations were available in the present study; this might have occurred by chance because of the small number of patients included. Infants with SCN5A mutations, however, should be included in a future study.

This study also had some other limitations. First, the number of LQTS infants was small and the present study did not include any infants who later died of SIDS or who were at risk for SIDS, although several previous studies have explained the absence of patients with SCN5A mutations. In the present study, we might have observed a risk for SIDS infants and the patients diagnosed in the infantile period. No data that can explain the absence of patients with SCN5A mutations were available in the present study; this might have occurred by chance because of the small number of patients included. Infants with SCN5A mutations, however, should be included in a future study.

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A combination of two major risk factors may be responsible for the development of life-threatening arrhythmia in LQTS infants: longest QTc and autonomic imbalance; and undeveloped parasympathetic activity and accentuated sympathovagal balance, during night-time sleep in early infancy. To prevent sudden infant death from QT prolongation, screening of infants with prolonged QT interval in early infancy is essential because β-blocker therapy is known to shorten QT interval and to decrease LQTS-related symptoms, although strategies to screen infants with QT prolongation are still controversial.

Conclusions

The authors declare no conflicts of interest.

Disclosures

References


**Supplementary Files**

**Supplementary File 1**

**Table S1.** HR vs. time of day, sleep and LQTS status

**Table S2.** QTc and HRV correlations in early infancy vs. LQTS status

Please find supplementary file(s); http://dx.doi.org/10.1253/circj.CJ-18-0048