Electrocardiographic Screening of 1-Month-Old Infants for Identifying Prolonged QT Intervals

Running title: Yoshinaga et al.; ECG screening of 1-month-old infants for LQTS

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Abstract:

**Background** - Neonatal electrocardiographic (ECG) screening is used to screen infants with prolonged QT intervals, as previously shown in Caucasians. However, this procedure needs to be confirmed in other ethnic groups.

**Methods and Results** - In 8 areas in Japan, an ECG was recorded in 4285 infants at 1-month medical checks. A prospective study showed that a provisional criterion of QTc ≥470 ms was appropriate for infants. To assess the validity of the criterion, all infants with a QTc between 460 and 470 ms were also followed. Five infants had a QTc ≥470 ms. Four infants were diagnosed with prolonged QT intervals from follow-up ECGs. Four infants showed no symptoms and did not have a family history of long QT syndrome. Two infants showed progressive prolongation of QT intervals and medication was started. Genetic testing was performed in 3 of 4 infants with prolonged QT intervals, and it revealed a KCNH2 mutation (3065 delT, L1021fs+34X) in 1 infant. One infant with a QTc ≥470 ms and 2 infants with a QTc between 460 and 470 ms showed a decline in their QTc values during follow-up. The study screened another infant with Wolff-Parkinson-White syndrome who was diagnosed with non-compaction before symptoms appeared.

**Conclusions** - Neonatal ECG screening can identify infants likely to be affected by long QT syndrome in the Japanese population, as already shown in Caucasians. This screening may also be useful for other important cardiac diseases.

**Key words:** long QT syndrome, sudden cardiac death, arrhythmia, electrocardiography, screening
Long QT syndrome (LQTS) is characterized by prolonged ventricular repolarization with a prolonged QT interval on the surface electrocardiogram (ECG). The clinical presentation of LQTS is the occurrence of syncope or cardiac arrest in children and young adults.\textsuperscript{1,2} Patients with LQTS who experience aborted cardiac arrest during infancy are at high risk for subsequent aborted cardiac arrest or death during their next 10 years,\textsuperscript{3} indicating that these patients are an extremely high-risk subset.

Sudden infant death syndrome (SIDS) is one of the major causes of death in infancy with the highest prevalence at approximately 2 months of age.\textsuperscript{4-6} SIDS is multi-factorial in origin,\textsuperscript{7} however, genetic studies have shown that approximately 10\% of cases diagnosed as SIDS carry functionally significant genetic mutations in LQTS genes.\textsuperscript{8,9}

Electrocardiographic (ECG) screening in infancy may permit early detection of a substantial percentage of patients at risk for SIDS.\textsuperscript{10} Studies of infants during infancy in Italy and a recent study in Japan have shown that corrected QT (QTc) intervals were longest at approximately 2 months of age.\textsuperscript{11,12} A large study conducted in Italy showed that the prevalence of LQTS might be close to 1:2,000,\textsuperscript{13} however, no studies have been conducted outside Europe. In Japan, medical examinations during infancy are mandatory and medical examinations at 1 month of age are currently performed for all infants. Therefore, the aim of the present study was to confirm that ECG screening of 1-month-old infants is able to identify Japanese infants with prolonged QT intervals, as previously shown in Caucasians.

Methods

Study population

The study was conducted in 16 maternity institutes in 8 areas between July 2010 and March 2011 in Japan, including Kagoshima, Fukuoka, Nagoya, Ogaki, Tokyo, Tochigi, Tsukuba, and Niigata.
The parents were asked to participate in the study at discharge from the maternity institutes. A total of 4319 consecutive infants participated in the study at the time of a 1-month medical check after obtaining written informed consent from parents. We obtained permission to use and analyze these data from the Ethics Committee of the National Hospital Organization Kagoshima Medical Center under the condition that the confidentiality of all personal data would be maintained.

Analysis of ECG and measurement of the QT interval

Twelve-lead ECGs were recorded at a speed of 25 mm/s with a FCP-4510 recorder (Fukuda Denshi, Tokyo, Japan). The ECGs were initially read in each center, and a written report was sent to parents of each participant. The ECGs were then transferred to one author (MY) of the present study, and all QT/RR data for the present study were re-measured by the same author (MY). The QT intervals of 3 consecutive beats were measured from the onset of the Q wave to the end of the T wave in lead V5. When the QT interval could not be measured because of instability of isoelectronic levels in lead V5, the QT intervals in lead II were measured. When a notch was present in more than 3 leads\textsuperscript{14,15} and this notch appeared at the same timing,\textsuperscript{16} the T wave was defined as a bifid T wave. The QT/RR data for each of 3 consecutive beats were corrected, and the mean values for the 3 consecutive QTc were used.

Screening and follow-up of infants with LQTS in a preliminary study

Published diagnostic criteria using the QTc by Bazett’s formula recommend additional diagnostic caution when scaling with tachycardic patients.\textsuperscript{14} In a preliminary study, a formula to minimize the effect of heart rate for infants was used: \textsuperscript{12} QTc = QT/RR\textsuperscript{0.43} and a provisional criterion of QTc \geq 440 ms\textsuperscript{0.43} were used.\textsuperscript{12} To assess the validity of the criterion, all infants with QTc \geq 430 ms and QTc < 440 ms were followed. Infants with QTc \geq 420 ms and QTc < 430 ms
were also followed in the Kagoshima area where the chief investigator (MY) was working and where 56% of the total subjects were participated. The screened infants were followed for a 2- or 3-week interval.

**Screening of infants by using Bazett’s formula**

Because of the current and frequent use of Bazett’s formula in the clinical setting, the present study was re-conducted retrospectively using Bazett’s formula. The QTc values calculated by the formula in the preliminary study (QT/RR<sup>0.43</sup>) were highly associated with those calculated by Bazett’s formula (r=0.989, p<0.0001) (Figure 1). The QTc values of 440, 430, and 420 ms<sup>0.43</sup> used in the preliminary study corresponded to the QTc values calculated by Bazett’s formula of 470, 460, and 450 ms<sup>0.5</sup> (Figure 1). Based on this finding, the screening strategy in the re-conducted study included a provisional criterion of QTc ≥470 ms<sup>0.5</sup> to screen infants with a prolonged QT interval. To assess the validity of this criterion, all infants with QTc ≥460 ms and QTc <470 ms were followed. Infants with QTc ≥450 ms and QTc <460 ms were also followed in the Kagoshima area where the chief investigator (MY) was working and where 56% of the total subjects had participated. The screened infants were followed for a 2- or 3-week interval. The definition of infants with a prolonged QT interval in the present study was those whose prolonged QTc values were sustained during follow-up at a 2- or 3-week interval.

**Follow-up strategies of infants with prolonged QT intervals**

In a nation-wide study in Japan, patients with LQTS who showed life-threatening arrhythmias at the perinatal period and whose mutations were determined were mostly those with LQT2 or LQT3. The clinical course of these infants was favorable with administration of beta-blockers and mexiletine, and with pacemaker implantation or an implantable cardioverter-defibrillator. In this Japanese series, beta-blockers and mexiletine were co-administered to 7 of 11 infants with
LQT2, and to all 7 LQT3 infants. Beta-blockers and mexiletine were co-administered in the present study when the QTc values progressively increased and when the parents accepted medication for their infants.

In the preliminary ECG-screening program, thorough familial ECG recording and/or genetic testing was not mandatory. Performance of familial ECG screening and/or genetic testing was based on the judgment of the chief physicians.

Genetic analysis

Genomic DNA was isolated from blood after obtaining written informed consent. Genetic screening for LQT-1 (KCNQ1), -2 (KCNH2), -3 (SCN5A), -5 ( KCNE1), -6 (KCNE2), -7 ( KCNJ2), -9 ( CAV3), -10 (SCN4B), and -12 ( SNTA1) was performed by PCR and direct DNA sequencing. When abnormal hand/foot findings were present, screening for LQT-8 (CACNA1C) was planned.

The exons of LQT-4 (ANKB), LQT-10 (SCN4B), and LQT-11 (AKAP9) were not analyzed because there are no reported cases of these mutations in the Japanese population. Genomic DNA was isolated using a QIAmp DNA Blood Midi Kit (Qiagen, Gaithersburg, MD). PCR products were purified by AMPure (Beckman Coulter, Brea, CA). After treatment with the BigDye Terminator v1.1 Cycle Sequence Kit (ABI, Warrington, UK) and BigDye X Terminator™, direct sequencing was performed by the ABI3130x1 Genetic Analyzer (ABI).

Statistical Analysis

The most appropriate cut-off values to screen QT prolongation for 1-month-old infants from the present study were obtained by the positive predictive value (PPV) and negative predictive value (NPV).
Results

Final subjects

Of 4319 infants who participated in the study, a final total of 4285 subjects were enrolled for this retrospective study whose QT/RR data of 3 consecutive beats could be measured (2148 males, 2038 females; sex was not described in 100 infants). Of 34 infants excluded, 3 consecutive QT/RR data could not be obtained because of instability of isoelectric lines in 26 infants; however, their QTc values were normal based on 1 or 2 QT/RR data sets. Five infants with complete right bundle branch block and 3 infants with Wolff-Parkinson-White (WPW) syndrome were also excluded from the QT study.

QTc intervals of infants

The mean values of the QT interval, heart rate, and QTc intervals of male infants were: 253 ± 17 ms, 160 ± 16 beats per minute (bpm), and 410 ± 19 ms, respectively; those of female infants were 255 ± 17 ms, 158 ± 16 bpm, and 413 ± 19 ms, respectively; and those of all infants were 254 ± 17 ms, 159 ± 16 bpm, and 412 ± 19 ms, respectively. The mean QTc value of female infants was longer than that of male infants (p<0.0001).

Infants with prolonged QT intervals

Of 4285 infants, 5 infants had a QTc of ≥470 ms at the time of the 1-month screening (Table 1). Four infants (3 males and 1 female) were diagnosed with prolonged QT intervals from the follow-up ECGs (Figure 2). Of these 4 infants, 2 (Cases 1 and 2 in Figure 2) showed progressive prolongation of QT intervals (Figures 3 & 4). Propranolol and mexiletine were administered to these 2 infants. Two patients (Cases 3 and 4 in Figure 2) were followed without medication. Case 1 was the third child for the parent, and Cases 2, 3, and 4 were the first child for each parent. All 4 families had no family history of LQTS-related symptoms, including sudden cardiac death.
One male infant with a QTc of ≥470 and 2 female infants with a QTc between 460 and 470 ms showed a decline in their QTc values during follow-up (Figure 2). One female infant with a QTc between 460 and 470 ms was lost to follow-up. Of 2420 infants (56% of the final total subjects) who participated in the Kagoshima area, 21 infants (0.87%) had QTc values between 450 and 460 ms, and all infants showed a decrease in QTc values during follow-up.

Genetic analysis

Genetic analysis was performed in 3 of 4 infants with a prolonged QT interval (Cases 1, 2, and 3 in Figure 3), and it demonstrated a frame-shift type mutation in the KCNH2 gene (3065 delT, L1021fs+34X) in 1 infant (Case 2).

Cut-off values for screening QT prolongation for 1-month-old infants

Assuming that 4 of 4285 infants had prolonged QT intervals in the present study, the most appropriate cut-off value to screen QT prolongation for 1-month-old infants was 470 ms, and the next appropriate value was 460 ms (Table 2).

Infants with miscellaneous heart diseases

Of 4319 infants who participated in the study, including 4285 infants whose QTc values were analyzed, some infants were found to have miscellaneous heart diseases; one infant had left ventricular non-impaction (LVNC) and one had situs inversus totalis. A 43-day-old male infant was admitted to our hospital because of the presence of WPW syndrome. He appeared active, but his echocardiography revealed LVNC (Figure 5). His left ventricular ejection fraction and brain natriuretic peptide levels at the first visit were 50% and 89 pg/ml, respectively. He was followed for 2- or 3-week intervals, and he showed an ejection fraction of 50% to 60%. His ejection fraction showed a sharp decrease to less than 30% at 81 days old, but his general status was good. Medication was then started with carvedilol and enalapril. He is currently 28 months old. He had
experienced supraventricular tachycardia (SVT) several times since the age of 5 months. However, SVT was successively treated and he finally received catheter ablation twice to treat SVT. His ejection fraction has recovered to 65% with medication (carvedilol, enalapril, and flecainide).

Discussion

The present study confirmed that ECG screening of 1-month-old infants is successful in identifying infants with prolonged QT intervals in the Japanese population, which is similar to findings in Caucasians. This screening was also able to identify an infant with life-threatening heart disease during the asymptomatic period.

A large study conducted in Italy showed that 17 infants among a cohort of 44,596 neonates were affected by LQTS, and that the prevalence of LQTS was 1:2,534 in Caucasians. Of 17 infants, 16 were diagnosed with LQTS because of the presence of both QT prolongation and disease-causing mutations, and one was diagnosed because the father of the infant with a QTc of 482 ms also had an extremely prolonged QTc (581 ms). The authors of this previous study hypothesized that the prevalence of LQTS is close to 1:2,000, considering the presence of some infants without genetic analysis in the study. The present study was conducted in the Japanese population. The distribution of infants with a QTc >470 ms was 5 of 4285 (0.12%) in the present study and 31 of 43,080 (0.07%) in a previous study, and that of a QTc between 460 and 470 ms was 3 of 4285 (0.07%) in the present study and 28 of 43,080 (0.06%) in a previous study. The distribution was not different between the present study and this previous study (p=0.38 and p>0.99, respectively).

The mean QTc intervals were similar between the 2 studies (412±19 ms in the present study and 406±20 ms in a previous study). The reason for slightly longer QTc values in the
present study than in the previous study\textsuperscript{13} might be due to the dates of the ECG recording. ECGs were recorded at 1 month old in the present study and between the 15th and 25th days of life in the previous study\textsuperscript{13}. Mean QTc intervals increase from birth to 2 months of age.\textsuperscript{11,12} Finally, 4 infants had prolonged QT intervals in the present study. These data suggest that neonatal ECG screening is successful for identifying infants with prolonged QT intervals in the Japanese population, as already shown in Caucasians.

QTc values in female children are known to be longer than those in male children, as well as in adolescents and the adult population. Accordingly, LQTS diagnostic criteria recommend using different criteria between males and females.\textsuperscript{1} A previous study showed that QTc values were not different between 4867 males and 4858 females on the third to fourth day of life (401 ± 19 vs 400 ± 20 ms; \( p = \text{not significant} \)).\textsuperscript{18} Another large study showed a sex difference in QTc values among 22 967 males and 21 629 females between the 15th and 25th day of life (405 ± 20 vs 407 ± 20 ms, \( p<0.001 \)).\textsuperscript{13} In the present study, a sex difference was also present on the 32nd day of life (410 ± 19 vs 413 ± 19 ms, \( p<0.001 \)). However, guidelines of the International Conference on Harmonization (ICH) reported that concerning the difference in the QT/QTc values in a thorough QT/QTc study, the threshold level of regulatory concern is approximately 5 ms, as evidenced by an upper bound of the 95% confidence interval around the mean effect on QTc of 10 ms.\textsuperscript{19} This suggests that a difference in QTc of a few ms between male and female infants is clinically irrelevant.

Of 4319 infants who participated in the study, including 4285 infants whose QTc values were analyzed, some infants were found to have miscellaneous heart diseases that were different from QT prolongation. Of these, echocardiography revealed a 43-day-old male infant with WPW syndrome, LVNC, and heart failure. He showed a sudden decrease in his ejection fraction to less
than 30% at 81 days old, although his general status still appeared to be good. Clinical manifestations of LVNC are highly variable, ranging from no symptoms to disabling congestive heart failure, even from the neonatal period.\textsuperscript{20} Children who are diagnosed with LVNC during infancy are at high risk for severe heart failure and a poor prognosis.\textsuperscript{21} Quaglini et al reported that ongoing neonatal ECG screening in over 30,000 infants identified infants with prolonged QT intervals, as well as 4 cases of asymptomatic life-threatening congenital heart disease, 3 cases of coarctation of the aorta, and 1 of anomalous origin of the left coronary artery from the pulmonary artery, which escaped detection at the initial medical visit.\textsuperscript{22} The results from this previous study and the present data indicate that neonatal ECG screening for QT prolongation, which was the primary objective of both studies, has additive value to screening.

\textbf{Limitations}

There are limitations to the present study. We did not perform genetic analysis of several infants with QTc of \textgreater{}460.\textsuperscript{13} We are not able to exclude the possibility that some of these infants have LQTS-related mutations. They should be re-studied in the future, although the valid time for re-examination is unclear. Fortunately, nation-wide school-based ECG screenings are mandatory for children and adolescents in the 1st, 7th, and 10th grades in Japan. These periods might contain candidates for re-examinations in Japan.

Finally, cost-effective analysis was not performed in the present study. However, neonatal ECG screening is reported to be highly cost-effective, and a significant number of lives can be saved.\textsuperscript{22} A cost-effective analysis of neonatal ECG screening should be performed in each country, because medical costs are different among countries.\textsuperscript{23}

\textbf{Implications}

The data of the present study might be useful for proposing candidates for screening criteria of a
prolonged QT interval in 1-month-old infants. We found that a QTc of \( \geq 470 \) ms was the best cut-off to screen infants with prolonged QT intervals, with a PPV of 80% and NPV of 100%. Candidate criteria could be 460 ms from the view point that the risk of the presence of false-negative cases should be avoided (PPV and NPV of 57% and 100%, respectively). However, a common concern in relation to ECG screening is that if there are too many false positives, this would generate undue anxiety in children and parents.\(^{24}\) However, even when we use the candidate value of 460 ms, the rate of false positives may be low (i.e., 0.5 per 1000). In an Italian study,\(^{13}\) the screening rate was 1.37 per 1000 infants (59 of 43 080 infants) with a cut-off value of \( \geq 460 \) ms. Of 42 infants whose QTc values were \( \geq 460 \) ms and in whom genetic testing was performed, 16 infants were diagnosed as LQTS genetically. The yield of genetic testing of clinically-diagnosed LQTS patients with QTc \( \geq 440 \) ms is generally 60%,\(^{25}\) suggesting that 27 (16 divided by 0.60) of 42 infants (64%) can be diagnosed as LQTS clinically. The rate of false positives was 0.49 per 1000 \( [1.37 \times (1 - 0.64)] \) in the Italian study.\(^{13}\) These candidate values should be validated in future studies.

**Conclusions**

Neonatal ECG screening can identify infants likely to be affected by LQTS in different ethnic groups, as shown in Caucasians, and might be useful for identifying other important cardiac diseases.

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**Conflict of Interest Disclosures:** None
References:


Table 1 Distribution of infants based on the duration of QT intervals in the present study and in an Italian study.13

<table>
<thead>
<tr>
<th>Duration of QT Intervals</th>
<th>Present Study</th>
<th>Italian Study13</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥470 ms</td>
<td>5 (0.12 %)</td>
<td>31 (0.07 %)</td>
</tr>
<tr>
<td>460-470 ms</td>
<td>3 (0.07 %)</td>
<td>28 (0.06 %)</td>
</tr>
<tr>
<td>450-460 ms</td>
<td>34 (0.79 %)</td>
<td>177 (0.41 %)</td>
</tr>
<tr>
<td>440-450 ms</td>
<td>172 (4.01 %)</td>
<td>858 (1.99 %)</td>
</tr>
<tr>
<td>&lt;440 ms</td>
<td>4071 (95.0 %)</td>
<td>41 986 (97.5 %)</td>
</tr>
</tbody>
</table>

The data are expressed as absolute values and percentages in parentheses. Electrocardiograms in the present study were recorded at 1 month old medical checks and those in the Italian study were recorded between 15 and 25 days old.

Table 2 Positive predictive value (PPV) and negative predictive value (NPV)

<table>
<thead>
<tr>
<th>QTc (ms)</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>430</td>
<td>0.0053</td>
<td>1.0000</td>
</tr>
<tr>
<td>440</td>
<td>0.0172</td>
<td>1.0000</td>
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<tr>
<td>450</td>
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<td>0.5714</td>
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<td>470</td>
<td>0.8000</td>
<td>1.0000</td>
</tr>
<tr>
<td>480</td>
<td>0.7500</td>
<td>0.9998</td>
</tr>
<tr>
<td>490</td>
<td>1.0000</td>
<td>0.9991</td>
</tr>
</tbody>
</table>

Figure Legends:

Figure 1. Association of QTc values calculated by the original formula with those calculated by Bazett’s formula.

QTc values calculated by the formula in a preliminary study (QT/RR0.43) were highly associated with those by Bazett’s formula (QT/RR0.5).
Figure 2. Time course of QTc values of infants whose QTc was longer than 460 ms.

Among 5 infants with a QTc >470 ms, Cases 1 (●) and 2 (●) received medication because of progressive prolongation of their QTc values, Cases 3 (■) and 4 (▲) were followed without medication, and in 1 infant (○), the QTc value was decreased. Among 3 infants with a QTc value between 460 and 470 ms, 1 infant was lost to follow-up.

Figure 3. An ECG of a Holter recording at 51 days old in an infant who received medication. The QTc value was 511 ms.

Figure 4. An ECG at 4 months old in a patient with a KCNH2 mutation. The QTc value was 533 ms.

Figure 5. An ECG (a) and images of echocardiography (b) in an infant. His ECG shows WPW syndrome and echocardiography shows non-compaction of the left ventricle.
QTc values (ms^{0.43}) by Bazett’s formula

\[ n = 4.285 \]
\[ r = 0.989 \]
\[ p < 0.0001 \]
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SUPPLEMENTAL MATERIAL
APPENDIX

List of maternity hospitals participating in the study;

(Kagoshima Area) Aiiku Hospital, Nobori Hospital, Ijuin Hospital Obstetrics & Gynecology, Hirano Angel Clinic, Mammy Clinic Ijuin, Kagoshima University Hospital, and National Hospital Organization Kagoshima Medical Center

(Fukuoka Area) Toono Obstetrics & Gynecology

(Nagoya Area) Futaba Clinic

(Ogaki Area) Ogaki Municipal Hospital

(Tokyo Area) Kyoritsunarashinodai Hospital, Aiwa Hospital, and Nihon University Itabashi Hospital

(Tochigi Area) Kimura Clinic

(Tsukuba Area) University of Tsukuba Hospital

(Niigata Area) Royal Heart Clinic
Figure. Distribution of infants based on the duration of QT intervals in the present study (A) and in the Italian study\textsuperscript{13} (B). The present study included 4285 infants at the one-month-old medical checks and the Italian study included 43 080 Caucasian infants of 15 to 25 days old. The format of Figures A and B was the same as Figure 1 in Reference 13. Absolute numbers and percentages are shown.