

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

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Background—Neonatal electrocardiographic screening is used to screen infants with prolonged QT intervals, as previously shown in whites. 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 checkup. 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 followed up. 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 noncompaction before symptoms appeared.

Conclusions—Neonatal electrocardiographic screening can identify infants likely to be affected by long-QT syndrome in the Japanese population, as already shown in whites. This screening may also be useful in identifying other important cardiac diseases. (*Circ Arrhythm Electrophysiol.* 2013;6:932-938.)

Key Words: arrhythmias, cardiac ■ death, sudden, cardiac ■ diagnosis ■ electrocardiography ■ long-QT syndrome

Long-QT syndrome (LQTS) is characterized by prolonged ventricular repolarization, with a prolonged QT interval on the surface ECG. The clinical presentation of LQTS is the occurrence of syncope or cardiac arrest in children and young adults.^{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,³ indicating that these patients are an extremely high-risk subset.

Clinical Perspective on p 938

Sudden infant death syndrome is one of the major causes of death in infants, with the highest prevalence at ≈ 2 months of age.⁴⁻⁶ Sudden infant death syndrome is multifactorial in origin⁷; however, genetic studies have shown that $\approx 10\%$ of cases diagnosed as sudden infant death syndrome carry functionally significant genetic mutations in LQTS genes.^{8,9}

Electrocardiographic screening in infants may permit early detection of a substantial percentage of patients at risk for

sudden infant death syndrome.¹⁰ Studies of infants in Italy and a recent study of infants in Japan have shown that QTc intervals were longest at ≈ 2 months of age.^{11,12} A large study conducted in Italy showed that the prevalence of LQTS might be close to 1:2000¹³; 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 on all infants. Therefore, the aim of the present study was to confirm whether electrocardiographic screening of 1-month-old infants identifies Japanese infants with prolonged QT intervals, as previously shown in whites.

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

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institutes. A total of 4319 consecutive infants participated in the study at the time of a 1-month medical checkup 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 an FCP-4510 recorder (Fukuda Denshi, Tokyo, Japan). The ECGs were initially read in each center, and a written report was sent to the parents of each participant. The ECGs were then transferred to 1 author (M.Y.) of the present study, and all QT/RR data for the present study were remeasured by the same author (M.Y.). 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 V_5 . When the QT interval could not be measured because of instability of isoelectronic levels in lead V_5 , the QT intervals in lead II were measured. When a notch was present in >3 leads^{14,15} and this notch appeared at the same timing,¹⁶ the T wave was defined as bifid. The QT/RR data of each of 3 consecutive beats were corrected, and the mean values of 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 the Bazett formula recommend additional diagnostic caution when scaling with tachycardic patients.¹⁴ In a preliminary study, a formula to minimize the effect of heart rate in infants was used¹²: $QTc = QT/RR^{0.43}$ and a provisional criterion of $QTc \geq 440$ ms^{0.43} were used.¹² To assess the validity of the criterion, all infants with $QTc \geq 430$ ms and $QTc < 440$ ms were followed up. Infants with $QTc \geq 420$ ms and $QTc < 430$ ms were also followed in the Kagoshima area where the chief investigator (M.Y.) was working and where 56% of the total subjects participated. The screened infants were followed for 2 or 3 weeks.

Screening of Infants Using the Bazett Formula

Because of the current and frequent use of the Bazett formula in the clinical setting, the present study was reconducted retrospectively using the Bazett formula. The QTc values calculated by the formula in the preliminary study ($QT/RR^{0.43}$) were highly associated with those calculated by the Bazett formula ($r=0.989$; $P<0.0001$; Figure 1). The QTc values of 440, 430, and 420 ms^{0.43} used in the preliminary study corresponded to the QTc values of 470, 460, and 450 ms^{0.5} calculated by the Bazett formula (Figure 1). Based on this finding, the screening strategy in the reconducted study included a provisional criterion of $QTc \geq 470$ ms^{0.5} to screen infants with a prolonged QT interval. To assess the validity of this criterion, all infants with $QTc \geq 460$ ms and

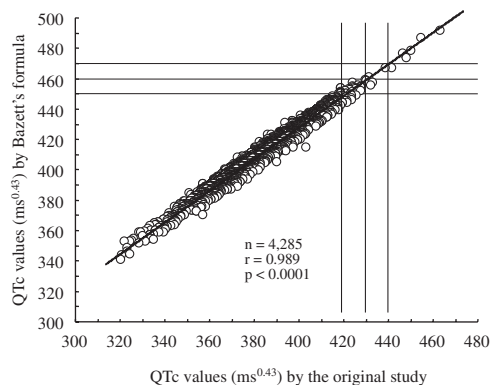


Figure 1. Association of QTc values calculated by the original formula with those calculated by the Bazett formula. QTc values calculated by the formula in a preliminary study ($QT/RR^{0.43}$) were highly associated with those by the Bazett formula ($QT/RR^{0.5}$).

$QTc < 470$ ms were followed up. Infants with $QTc \geq 450$ ms and $QTc < 460$ ms were also followed in the Kagoshima area where the chief investigator (M.Y.) was working and where 56% of the total subjects participated. The screened infants were followed for 2 or 3 weeks. 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 nationwide 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 LQT3.¹⁷ The clinical course of these infants was favorable with administration of β -blockers and mexiletine and with pacemaker implantation or an implantable cardioverter-defibrillator. In this Japanese series, β -blockers and mexiletine were coadministered to 7 of 11 infants with LQT2 and to all 7 LQT3 infants.¹⁷ β -Blockers and mexiletine were coadministered in the present study when the QTc values progressively increased and when the parents accepted medication for their infants.

In the preliminary electrocardiographic screening program, thorough familial electrocardiographic recording and genetic testing were not mandatory. The performance of familial electrocardiographic screening and 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 polymerase chain reaction 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 QIAamp DNA Blood Midi Kit (Qiagen, Gaithersburg, MD). Polymerase chain reaction products were purified by AMPure (Beckman Coulter, Brea, CA). After treatment with the BigDye Terminator v1.1 Cycle Sequencing Kit (ABI, Warrington, United Kingdom) and BigDye X Terminator, direct sequencing was performed by the ABI3130x1 Genetic Analyzer (ABI).

Statistical Analysis

The most appropriate cutoff values to screen for QT prolongation in 1-month-old infants in the present study were obtained from the positive predictive value and negative predictive value.

Results

Final Subjects

Of the 4319 infants who participated in the study, a total of 4285 subjects were enrolled in this retrospective study whose QT/RR data of 3 consecutive beats could be measured (2148 male infants, 2038 female infants; sex was not described in 100 infants). Of the 34 infants excluded, 3 consecutive QT/RR data could not be obtained because of the 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 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, and 410 ± 19 ms, respectively; those of female infants

were 255 ± 17 ms, 158 ± 16 beats per minute, and 413 ± 19 ms, respectively; and those of all infants were 254 ± 17 ms, 159 ± 16 beats per minute, 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 the 4285 infants, 5 infants had a QTc of ≥ 470 ms at the time of the 1-month screening (Table 1). Four infants (3 male infants and 1 female infant) 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 and 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 of the parent, and cases 2, 3, and 4 were the first children of their parents. 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 the 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 frameshift-type mutation in the *KCNH2* gene (3065 delT, L1021fs+34X) in 1 infant (case 2).

Cutoff Values for Screening for QT Prolongation in 1-Month-Old Infants

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

Infants With Miscellaneous Heart Diseases

Of the 4319 infants who participated in the study, including 4285 infants whose QTc values were analyzed, some infants

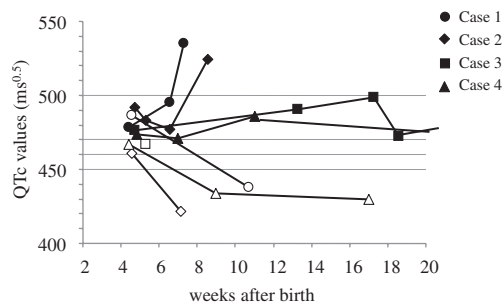


Figure 2. Time course of QTc values of infants whose QTc was >460 ms. Among 5 infants with a QTc >470 ms, cases 1 (●) and 2 (◆) received medication because of progressive prolongation of their QTc values, cases 3 (■) and 4 (▲) were followed without medication, and in 1 infant (○), the QTc value decreased.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

were found to have miscellaneous heart diseases; 1 infant had left ventricular nonimpaction (LVNC), and 1 had situs inversus totalis. A 43-day-old male infant was admitted to our hospital because of the presence of Wolff–Parkinson–White syndrome. He seemed 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 weeks, and he showed an ejection fraction of 50% to 60%. His ejection fraction showed a sharp decline to $<30\%$ at 81 days of age, but his general status was good. Medication was then started with carvedilol and enalapril. He is currently 28 months old. He experienced supraventricular tachycardia several times since the age of 5 months. However, supraventricular tachycardia was successively treated, and he finally received catheter ablation twice as a treatment for supraventricular tachycardia. His ejection fraction has recovered to 65% with medication (carvedilol, enalapril, and flecainide).

Discussion

The present study confirmed that electrocardiographic 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 whites.¹³ 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 1:2534 in whites.¹³ Of the 17 infants, 16 were diagnosed with LQTS because of the presence of both QT prolongation and disease-causing mutations, and 1 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 1:2000, considering the presence of some infants without genetic analysis in the study.¹³ 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 study¹³ 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

Table 1. Distribution of Infants Based on the Duration of QT Intervals in the Present Study and in an Italian Study¹³

| QTc, ms | Present Study | Italian Study |
|------------|---------------|----------------|
| ≥ 470 | 5 (0.12%) | 31 (0.07%) |
| 460–470 | 3 (0.07%) | 28 (0.06%) |
| 450–460 | 34 (0.79%) | 177 (0.41%) |
| 440–450 | 172 (4.01%) | 858 (1.99%) |
| <440 | 4071 (95.0%) | 41 986 (97.5%) |
| | 4285 (100%) | 43 080 (100%) |

The data are expressed as absolute values and percentages in parentheses. ECGs in the present study were recorded in infants at the 1-month medical checkup, and those in the Italian study were recorded in infants between 15 and 25 days of age.

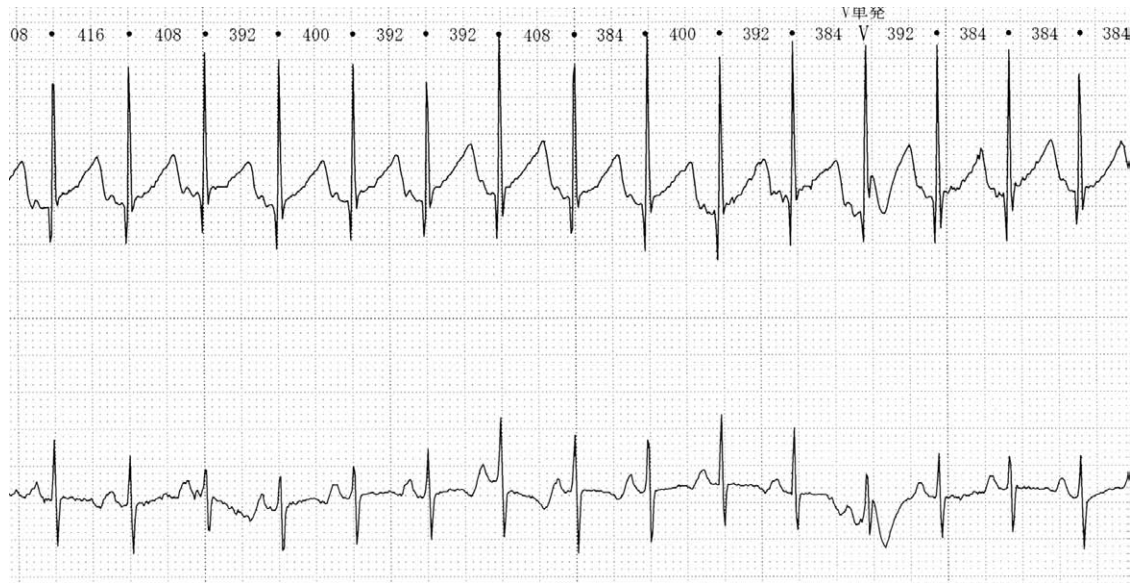


Figure 3. An ECG of a Holter recording at 51 days of age in an infant who received medication. The QTc value was 511 ms.

not different between the present study and this previous study ($P=0.38$ and $P>0.99$, respectively).¹³

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).¹³ The reason for slightly longer QTc values in the present study than in the previous study¹³ might be because of the dates of the electrocardiographic recording. ECGs were recorded in 1-month-old infants in the present study and between the 15th and 25th days of life in the previous study.¹³ Mean QTc intervals increase from birth to 2 months

of age.^{11,12} Finally, 4 infants had prolonged QT intervals in the present study. These data suggest that neonatal electrocardiographic screening is successful for identifying infants with prolonged QT intervals in the Japanese population, as already shown in whites.

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 male and female infants.¹ A previous study showed that QTc values were not

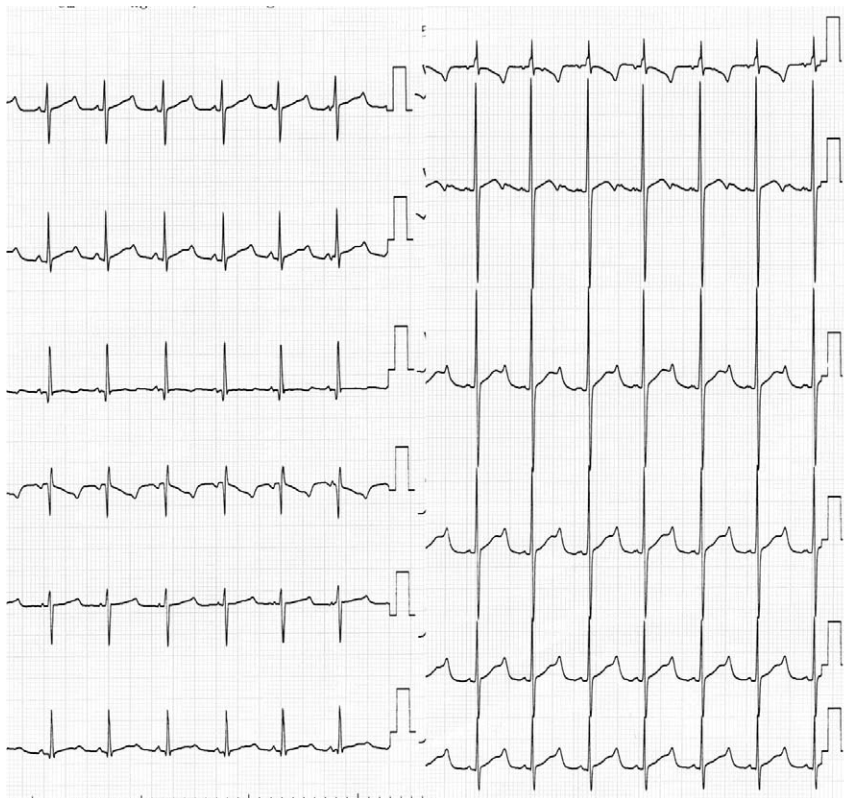


Figure 4. An ECG at 4 months of age in a patient with a *KCNH2* mutation. The QTc value was 533 ms.

Table 2. Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

| QTc, ms | PPV | NPV |
|---------|--------|--------|
| 430 | 0.0053 | 1.0000 |
| 440 | 0.0172 | 1.0000 |
| 450 | 0.0976 | 1.0000 |
| 460 | 0.5714 | 1.0000 |
| 470 | 0.8000 | 1.0000 |
| 480 | 0.7500 | 0.9998 |
| 490 | 1.0000 | 0.9991 |

different among 4867 male and 4858 female infants on the third to fourth day of life (401 ± 19 versus 400 ± 20 ms; $P=\text{not significant}$).¹⁸ Another large study showed a sex difference in QTc values among 22967 male and 21629 female infants between the 15th and 25th day of life (405 ± 20 versus 407 ± 20 ms; $P<0.001$).¹³ In the present study, a sex difference was also present on the 32nd day of life (410 ± 19 versus 413 ± 19 ms; $P<0.001$). However, guidelines of the International Conference on Harmonization reported that concerning the difference in the QT/QTc values in a thorough QT/QTc study, the threshold level of regulatory concern is ≈ 5 ms, as evidenced by an upper bound of the 95% confidence interval around the mean effect on QTc of 10 ms.¹⁹ This suggests that a difference in QTc of a few milliseconds between male and female infants is clinically irrelevant.

Of the 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 Wolff–Parkinson–White syndrome, LVNC, and heart failure. He showed a sudden decrease in his ejection fraction to $<30\%$ at 81 days of age, although his general status still seemed to be good. Clinical manifestations of LVNC are highly variable, ranging from no symptoms to disabling congestive heart failure, even from the neonatal period.²⁰ Children who are diagnosed with LVNC during infancy are at high risk for severe heart failure and a poor prognosis.²¹ Quagliani et al²² reported that ongoing neonatal electrocardiographic screening in $>30\,000$ 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 case of anomalous origin of the left coronary artery from the pulmonary artery, which escaped detection at the initial medical visit. The results from this previous study and the present data indicate that neonatal electrocardiographic screening for QT prolongation, which was the primary objective of both studies, has additive value to screening.

Limitations

There are limitations to the present study. We did not perform genetic analysis of several infants with QTc >460 ms.¹³ We are not able to exclude the possibility that some of these

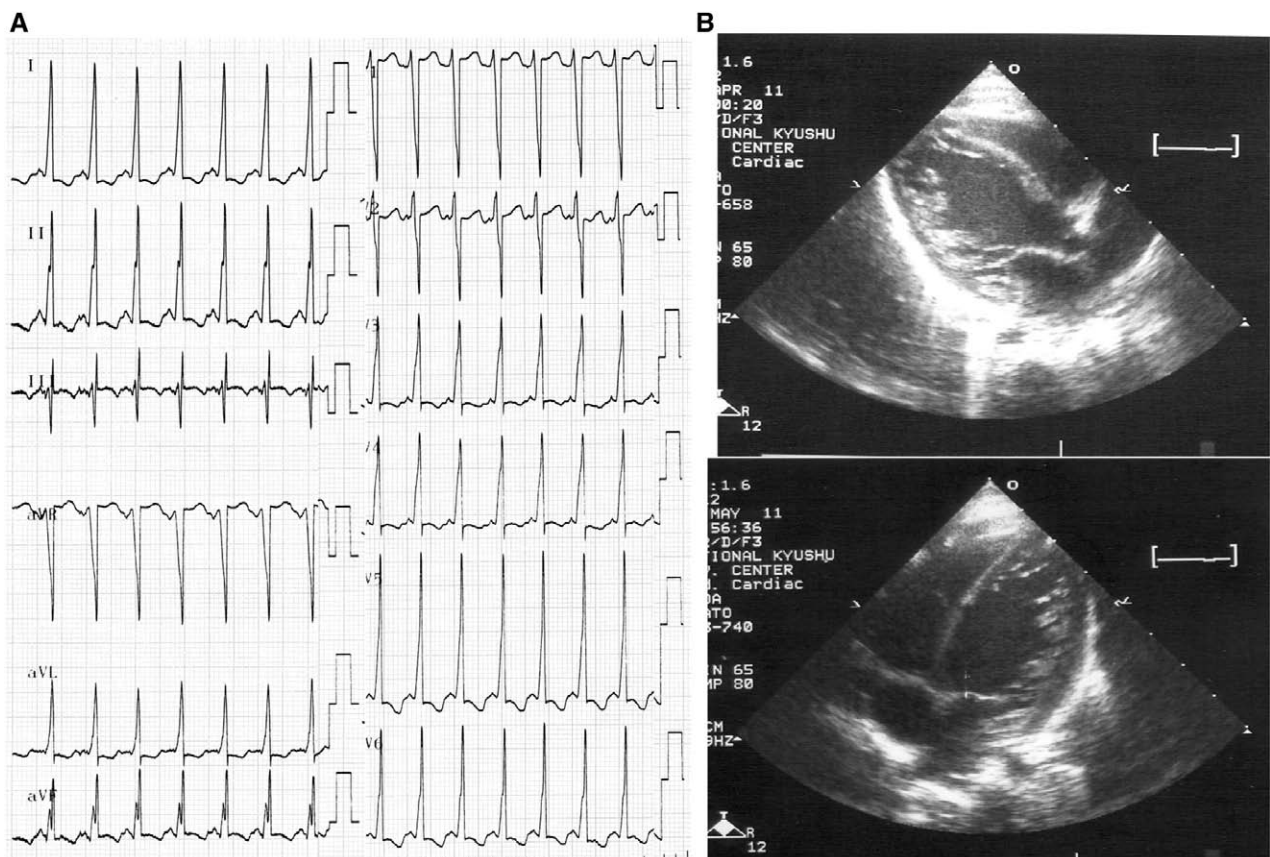


Figure 5. An ECG (A) and images of echocardiography (B) in an infant. His ECG shows Wolff–Parkinson–White syndrome, and echocardiography shows noncompaction of the left ventricle.

infants have LQTS-related mutations. They should be restudied in the future, although the valid time for re-examination is unclear. Fortunately, nationwide school-based electrocardiographic screenings are mandatory for children and adolescents in the first, seventh, 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 electrocardiographic screening is reported to be highly cost-effective, and a significant number of lives can be saved.²² A cost-effective analysis of neonatal electrocardiographic screening should be performed in each country because the medical costs are different among countries.²³

Implications

The data of the present study might be useful in proposing candidates for screening criteria of a prolonged QT interval in 1-month-old infants. We found that a QTc ≥ 470 ms was the best cutoff to screen infants with prolonged QT intervals, with a positive predictive value of 80% and negative predictive value of 100%. Candidate criteria could be 460 ms from the viewpoint that the risk of the presence of false-negative cases should be avoided (positive predictive value and negative predictive value of 57% and 100%, respectively). However, a common concern in relation to electrocardiographic screening is that if there are too many false-positives, and 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 (ie, 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 cutoff value of ≥ 460 ms. Of the 42 infants whose QTc values were ≥ 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 ≥ 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 electrocardiographic screening can identify infants likely to be affected by LQTS in different ethnic groups, as shown in whites, and might be useful in identifying other important cardiac diseases.

Sources of Funding

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Disclosures

None.

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CLINICAL PERSPECTIVE

This study aimed to determine whether electrocardiographic screening of 1-month-old infants identifies Japanese infants with prolonged QT intervals, as previously shown in whites. The prevalence of sudden infant death syndrome was 15 in 100 000 between 2005 and 2008 in Japan. Genetic studies have shown that $\approx 10\%$ of cases diagnosed with sudden infant death syndrome carry functionally significant genetic mutations in long-QT syndrome (LQTS) genes. The prevalence of sudden infant death syndrome may be higher because a thorough examination, including an autopsy, is needed to diagnose the syndrome. The prevalence of out-of-hospital cardiac arrest in infants was recently reported to be 41 in 100 000 between 2005 and 2008 in Japan. Italian studies showed that the prevalence of LQTS is close to 1:2000, mainly based on genetic data. In the present study, 2 of 4319 infants needed medication because their QTc values were progressively prolonged during several months of life. These data showed that 1:2000 infants (ie, 50 in 100 000 infants) have the LQTS genotype and phenotype. Patients with LQTS who experience symptoms during infancy are known to be at high risk for subsequent sudden cardiac death. Italian and Japanese studies have also found infants with life-threatening congenital heart disease during asymptomatic periods. These 2 studies in different ethnic groups showed that neonatal electrocardiographic screening can identify infants likely to be affected by LQTS and might be useful in identifying other important cardiac diseases. The cost-effectiveness and feasibility of neonatal electrocardiographic screening should be thoroughly evaluated worldwide as soon as possible.

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

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SUPPLEMENTAL MATERIAL

APPENDIX

List of maternity hospitals participating in the study;

(Kagoshima Area) Aiiiku Hosiptal, 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

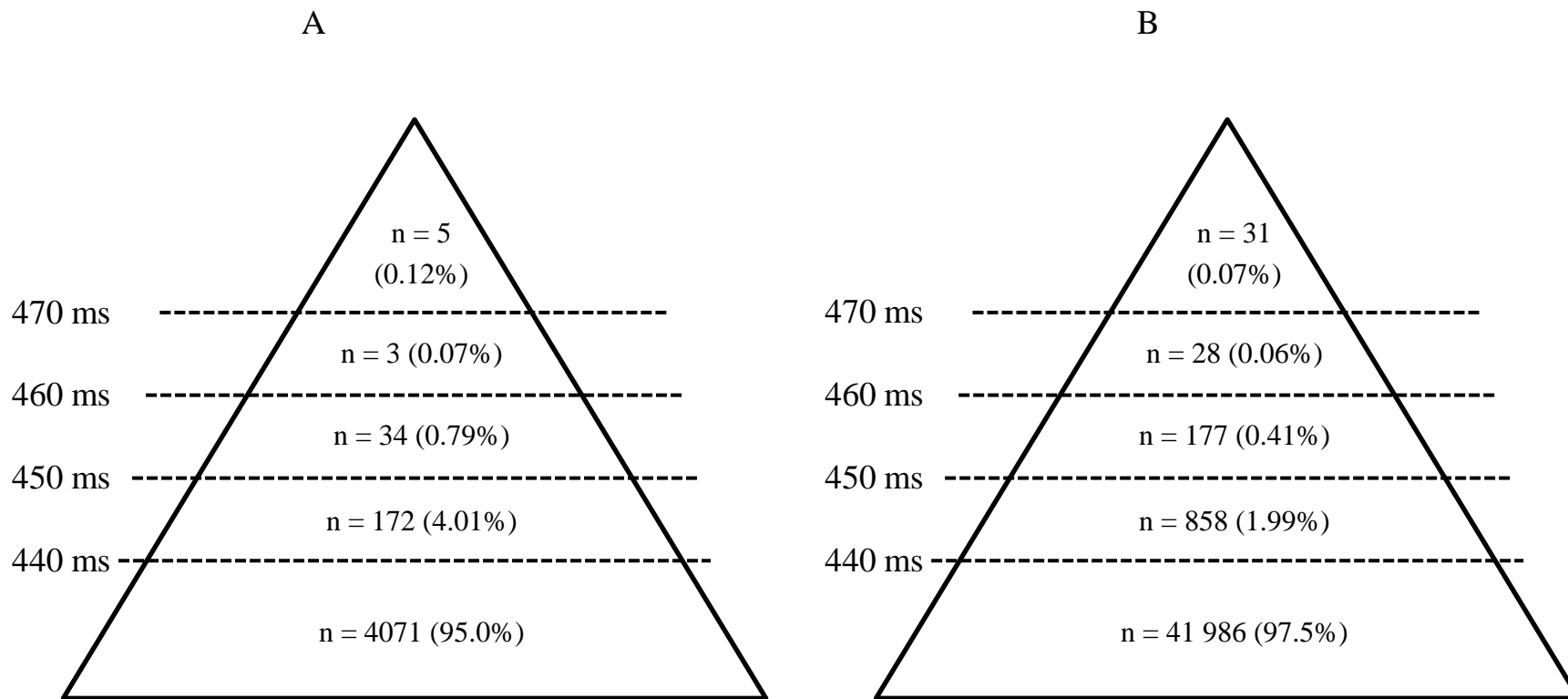


Figure. Distribution of infants based on the duration of QT intervals in the present study (A) and in the Italian study¹³ (B). The present study included 4285 infants at the one-month-old medical checks and the Italian study included 43 080 Caucasian infants of 15 to 25 days old. The format of Figures A and B was the same as Figure 1 in Reference 13. Absolute numbers and percentages are shown.