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Single-centre retrospective analysis of the best timing for the QTc interval length assessment in neonates

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ABSTRACT

Objective To evaluate the best timing for ECG screening in order to diagnose long QT syndrome and lower, at the same time, the false positives.

Design We retrospectively evaluated the corrected QT (QTc) interval in the clinical reports of the ECG screening performed, as per internal protocol.

Setting An outpatient setting in our Unit of Neonatology and Pediatrics, Santa Maria Goretti Hospital in Latina, Italy.

Patients We enrolled 3467 healthy neonates between 14 and 30 days of life.

Interventions The newborns with abnormal QTc interval were invited to subsequent revaluation every 21 days, until normalisation or necessity to refer to a tertiary paediatric cardiology centre.

Main outcome measures Difference in QTc according to patients' characteristics and number of false positives at second ECG evaluation.

Results At first evaluation, 249 (7.2%) newborns had prolonged QTc. We did not find any significant difference in the QTc length according to gestational age (p=0.40) and birth weight (p=0.81). As expected, girls had longer QTc than boys (p=0.01). Only 11 out of 240 (4.6%) and 1 out of 238 infants (0.4%) had persistently prolonged QTc at second and third ECG evaluation, respectively. The QTc decreased significantly at second (p<0.0001) and third evaluation (p=0.0035).

Conclusions In our study, we showed that a single screening performed in healthy infants after 60 days of life could reduce the risk of false positives, with a beneficial impact on public national health system and the chance to start early therapy in case of long QT syndrome.

What is known about the subject?

- Long QT syndrome is a known cause of sudden death infant syndrome and premature cardiac death in children, adolescents and young adults.
- Trying to find the best timing for ECG screening in infants is critical for the impact it could have on public health.
- Several studies have been published in multiple countries, questioning the role of paediatric mass ECG screening to prevent sudden death, but results are still controversial.

What this study adds?

- We showed that a single screening performed in healthy infants after 60 days of life could reduce the risk of false positives.

INTRODUCTION

Long QT syndrome (LQTS) is a genetically determined disease involving the heart's electrical system, characterised by prolonged corrected QT (QTc) interval and T wave abnormalities on the ECG. In children and young adults suffering from this condition, there is an increased risk of ventricular arrhythmias.[1] LQTS is a channelopathy associated with sudden infant death syndrome (SIDS), accounting for 5%–10% of cases.[2–6] The ECG represents the gold standard for the evaluation of QT interval: it is non-invasive, reproducible, with high sensitivity and low-cost/effectiveness.[7] Moreover, early ECG diagnosis is critical to start treatment in order to prevent life-threatening events, especially when the electrocardiographic alteration is associated with seizures or syncope.[7 8]

Several studies have been published in multiple countries, questioning the role of paediatric mass ECG screening to prevent sudden death, with controversial results.[8–11] Schwartz *et al*[12] found an association during ECG screening in the third or fourth day of life between prolonged QT interval in the first week of life and SIDS, but the percentage of false positives was high (99%). Thus, the authors suggested to screen newborns during the third or fourth week of life, before the peak of SIDS (2–6 months).[7] On the other hand, Hayashi *et al*[9] suggested to screen only school-age children at 1st, 7th and 10th grades (approximately at 6, 12 and 15 years old), as the risk of a cardiac event is higher in male children in this range of age.

In Italy, ECG screening is mandatory by law only for sports activities.[13] In order to identify the best timing to run ECG screening,

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we retrospectively evaluated the clinical reports of the neonates born in our hospital and had undergone electrocardiographic screening in an outpatient setting.

PATIENTS AND METHODS

Patient and public involvement

Patients were not involved in the design and recruitment of this study; every parent was informed only of the results of his/her child.

Study population

We analysed 3467 healthy neonates out of the 3581 healthy babies born from February 2018 to June 2020 in the Neonatology and Pediatrics Unit of the Santa Maria Goretti Hospital in Latina and referred to our service of paediatric cardiology for ECG screening. In our hospital, the internal protocol, according to Schwartz *et al*,[12] requires all healthy neonates to undergo an electrocardiographic evaluation in the first month of life. We enrolled all the healthy newborns with age between 14 and 30 days. The exclusion criteria were: any disease requiring neonatal intensive/subintensive care, history of perinatal asphyxia, concomitant treatments that could prolong QT, dyselectrolytemia and maternal history of autoimmune diseases.

ECG screening

Our study protocol at first evaluation, before 30 days of life, included:

1. Anamnesis for: gestational age (GA), birth weight (BW), first-degree and second-degree family history of congenital heart diseases and/or sudden death in infancy and early adulthood, concomitant medications, possible symptoms (hypotonia, tachypnoea, decreased level of consciousness, seizures, etc).
2. Cardiology visit, focused on exclusion of congenital heart diseases.
3. 12-lead standard ECG at paper speed of 25 mm/s (with ECG Nihon Kohden Cardiofax C). Heart rate was manually calculated as RR distance.[14] QT interval was manually calculated in leads II and V5, from the beginning of Q wave to the end of the T wave (ie, the intersection of a tangent to the steepest slope of the last limb of the T wave and the baseline).[14 15] QTc interval was calculated with the smartphone application 'Qx calculate', which uses the Bazett's formula.[16] Given the possibility of inaccuracy when calculating the QTc interval,[17] every calculation was separately performed by a cardiologist and a paediatrician, and the most prolonged of the two was taken in consideration. In addition, automatic QT readings were not used, given poor agreement with manual calculations.[18] We considered the following cut-offs for QT interval values: short if ≤340 ms; normal if >340 ms but <440 ms; prolonged borderline if ≥440 and<460 ms; prolonged pathological if ≥460 ms.[19–21]

After the first visit, all the newborns were divided in three groups: group I, newborns with normal QTc (>340 ms and <440 ms); group II, newborns with prolonged QTc (≥440 ms); and group III, newborns with short QTc (<340 ms).

Follow-up

After the first assessment, the subjects with pathological QTc interval (either prolonged or short) were invited to a second assessment after 3 weeks (at age of 5–7 weeks), to perform: (a) anamnesis for growth, feeding, possible symptoms (hypotonia, tachypnoea, decreased level of consciousness, seizures, etc); (b) 12-lead standard ECG as previously described.

The same patients were then invited to a third visit for anamnesis and 12-lead standard ECG after 3 weeks (at the age of 8–10 weeks). The ones with still pathological QTc interval at third evaluation were referred to a tertiary paediatric cardiology centre for ECG evaluation, genetic testing and, eventually, pharmacological treatment.

The parents of the patients who did not show for second or third evaluation were called in order to establish a new appointment.

Statistical analysis

The statistical analysis was performed with JMP V.14.3.0 program for Mac (SAS Institute), GraphPad Prism V.8.0 for MacOS (GraphPad, La Jolla, California, USA) and SPSS V.25.0 for MacOS (SPSS, IBM, Harmonk, New York, USA). For each variable, the normal distribution of the population was tested with D'Agostino-Pearson test to check whether parametric or non-parametric tests could be used for statistical analysis. Continuous variables were expressed as mean±SD or median with IQR according to sample distribution; nominal variables were expressed as percentage. To compare continuous variables across groups, Student's t-test, Mann-Whitney/Wilcoxon or Kruskal-Wallis test were performed according to sample distribution. For every test, the two-tailed p value was considered significant if <0.05.

RESULTS

We enrolled 3467 newborns: 1515 girls (43.7%) and 1952 boys (56.3%). Patients' main characteristics are found in table 1.

The distribution of QTc length at first, second and third evaluation, age, GA and BW was not normal (p<0.0001 for each variable). Skewness and kurtosis for each variable were: −0.57 and 1.05 for GA, −0.73 and 0.33 for BW, −0.59 and −0.85 for age, 0.37 and 0.46 for first QTc, 0.47 and 0.50 for second QTc, 0.75 and 0.25 for third QTc. The normal QQ plots can be found in figure 1. Therefore, for the statistical analysis of our data, we used only non-parametric tests.

Association between QTc and population characteristics at first evaluation

The entire population was divided in two groups according to QTc value at first ECG evaluation:

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Table 1 Population characteristics at first ECG evaluation

Variable	N (%)	Median (IQR)
Male	1939 (55.9)	
Female	1528 (44.1)	
QTc ≤340 ms	11 (0.3)	327 (11)
QTc 341–439 ms	3207 (92.5)	397 (58)
QTc 440–460 ms	239 (6.9)	443 (0)
QTc >460 ms	10 (0.3)	469 (41)
QTc (ms), Total		398 (30)
GA ≤36 weeks	315 (9.1)	36 (1)
GA 37–40 weeks	2798 (80.7)	39 (2)
GA >40 weeks	354 (10.2)	41 (0)
GA (weeks), Total		39 (2)
BW <2500 g	250 (7.2)	2300 (220)
BW 2500–4000 g	3013 (86.9)	3313 (500)
BW >4000 g	204 (5.9)	4200 (320)
BW (g), Total		3315 (590)
Positive family history	107 (3.1)	

BW, birth weight; GA, gestational age; QTc, corrected QT.

- Group I (3207 patients): QTc >340 ms but <440 ms.
- Group II (249 patients): QTc ≥440 ms.
- Group III (11 patients): QTc ≤340 ms.

We did not find any significant difference in the QTc length according to GA (397 (32.8) vs 397.5 (30) vs 399 (26) ms, p=0.40). Patients in group I did not have significant different BW than the babies in group II (3320 (580) vs 3300 (580) g, p=0.81). Females had significantly longer QTc than males (398 (29) vs 397 (33) ms, p=0.01).

Positive family history

From our records, we found a positive family history of congenital heart diseases in 90 (2.6%) neonates and of sudden death in infancy in 17 (0.5%) neonates. In these subgroups, nine (8.3%) had a prolonged QTc interval at first assessment, with a normalization at second ECG in eight of them. In addition, even for the last one, a normal QTc interval was recorded at third ECG evaluation. In fact, there was no statistically significant difference in QTc length according to family history at the first electrocardiographic assessment (positive family history 404 (22) vs negative family history 398 (30) ms; p=0.05).

ECG evaluation

The results of the ECG study are shown in figure 2. Unfortunately, the parents of the patients who skipped the second or third visit did not consent to establish a new appointment, even when adequately informed about the risks of LQTS.

At first ECG evaluation

We evaluated 3467 neonates; median GA was 39 (2) weeks, median BW was 3315 (590) g, median age was 26 (7) days and median QTc interval was 398 (30) ms.

The QTc interval evaluation showed:

- 3207 patients (92.5%) with normal QTc interval.
- 11 patients (0.3%) with short QTc interval.
- 249 patients (7.2%) with prolonged QTc interval.

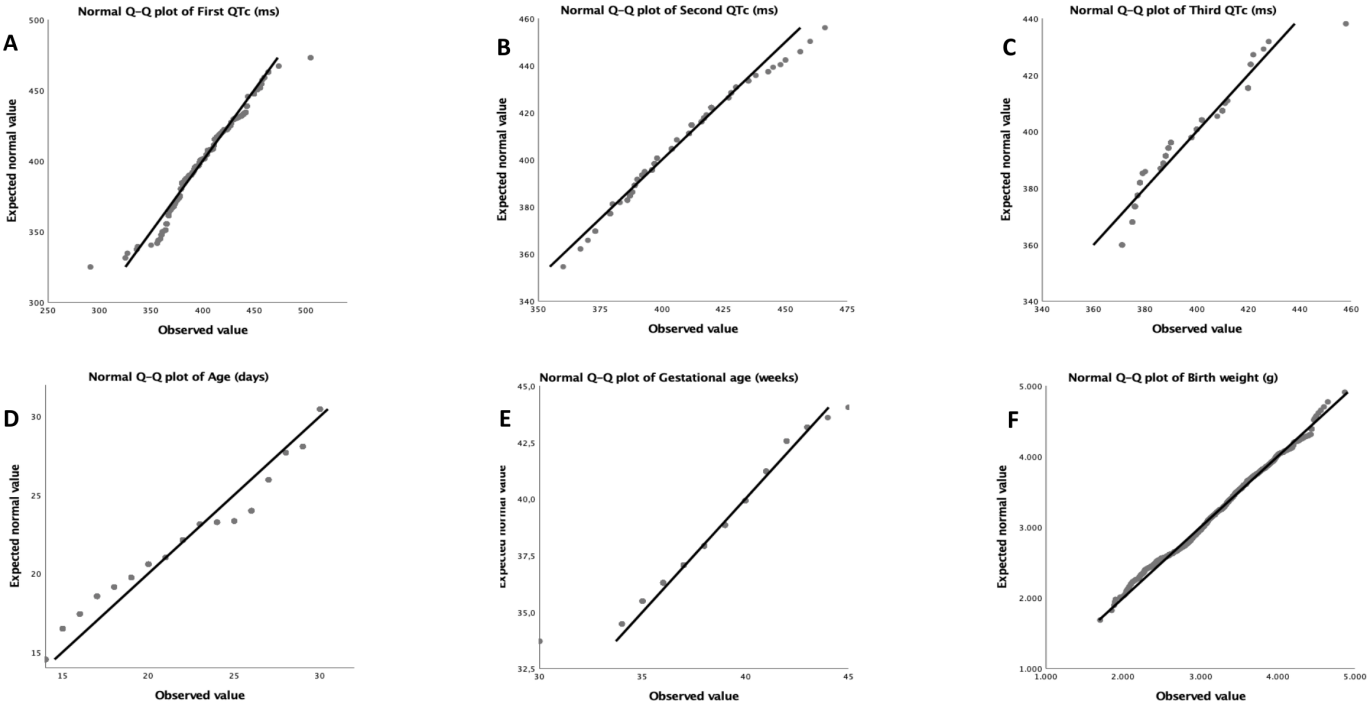

Figure 1 Normal QQ plots of QTc at (A) first, (B) second and (C) third evaluation, (D) age, (E) gestational age and (F) birth weight. QTc, corrected QT.

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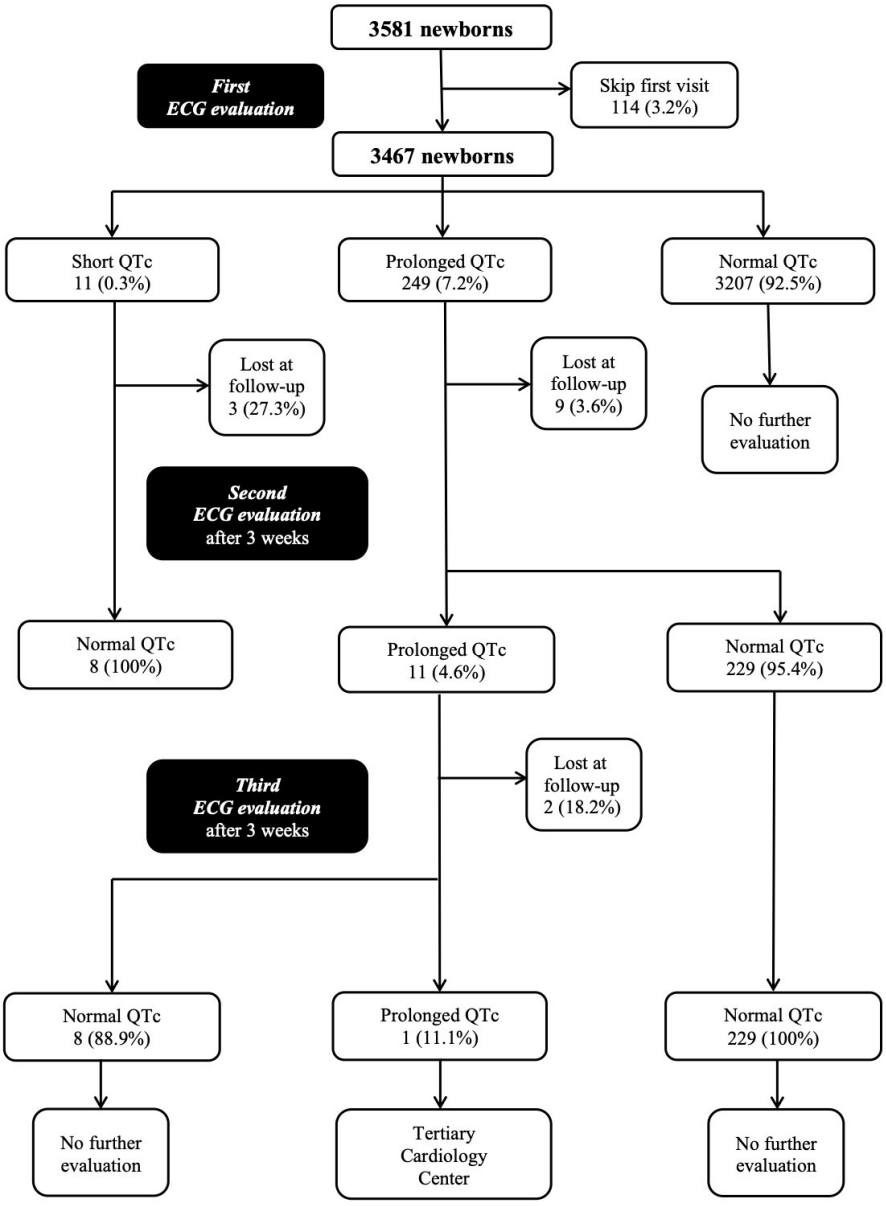

Figure 2 Analysis of the corrected QT interval (QTc) in the neonates of the study at the first, second and third ECG evaluation.

At second ECG evaluation

We enrolled 260 patients with pathological QTc interval at first ECG screening. Twelve patients (4.6%) were lost at follow-up due to skip to visit (three newborns with short QTc and nine with prolonged QTc). Median GA was 39 (3) weeks, median BW was 3300 (570) g, median age was 47 (6) days and median QTc interval was 404 (25) ms.

As regards the QTc interval evaluation, we found that:

- In all eight neonates with previous short QTc, there was a normalisation of the interval.
- Of 240 neonates with prolonged QTc, 229 had normal QTc and 11 had QTc persistently ≥440 ms.

Therefore, with respect to the diagnosis of LQTS only at the first ECG evaluation, the percentage of false positives was 95.4%, while true positives were 4.6% at the second evaluation.

In addition, in the subgroup with prolonged QTc (group II), the QTc recorded at second ECG after 3 weeks resulted significantly lower than the one measured at first ECG: the p value was <0.0001.

At third ECG evaluation

We enrolled 240 neonates found with prolonged QTc at first ECG assessment, as per internal protocol. Two subjects were lost at follow-up (skip to visit). Median GA was 39 (3) weeks, median BW was 3300 (560) g, mean age was 67 (6) days and mean QTc interval was 389 (32) ms.

As regards the QTc interval assessment, we found that only one patient (9% of those with prolonged QTc at second ECG) had persistent prolonged QTc (QTc=458 ms). The QTc at third evaluation resulted lower than the ones recorded at first (p<0.0001) and second evaluation (p=0.0035).

This infant was then referred to a tertiary cardiology centre for further evaluation. A fourth ECG assessment

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performed by the tertiary centre, 3 weeks later, showed a normal QTc interval, while the genetic test is still ongoing.

DISCUSSION

In our study, we did not find any association between QTc and BW, GA and positive family history for congenital heart disease or sudden death in infancy. As previously reported,[22] females had slightly longer QTc than males. Nonetheless, it is important to consider that, in case of history of LQTS in parents, given the possible autosomal dominant transmission, a prolonged QTc could be encountered in 50% of their children.[13] Therefore, in the case of family history of LQTS, SIDS or sudden death, the ECG screening should be performed in the first 30 days of life.

ECG screening during infancy is still on debate; on one hand some authors[7] report great cost-effectiveness of mass ECG screening, while, on the contrary, others[11] state that a clinical registry and a cascade tracing could be the best strategy.

We think that mass ECG screening in newborns is helpful for public health, but only when performed at the right time. A too early ECG screening leads, as described by Schwartz *et al*,[12] to a major percentage of false positives. The same author, to avoid this low specificity, identified the third and fourth weeks of life as the best timing for ECG screening.[8 20] A similar indication is proposed by the European Society of Cardiology.[19] We found that: at first ECG 249 (7.2%) of 3467 patients had QTc prolongation, at the second ECG only 11 (4.6%) of 240 patients resulted true positives and at the third screening only 1 neonate had a prolonged QTc, with normalisation at the fourth check in a tertiary paediatric cardiology centre.

Therefore, we suggest performing the electrocardiographic screening later, around 60 days of life, with the exception of children with family history of LQTS or short QT syndrome, in order to avoid an excessive number of false positives and higher costs. On one hand, it is important, when performing the screening, to exclude any possible confounder, such as perinatal asphyxia, concomitant treatments, dyselectrolytemia and maternal history of autoimmune diseases, as suggested by Schwartz *et al*.[19] On the other hand, it is known that in the first weeks of life, QTc prolongation is, at least, possible.[23] Since crude birth rate in Italy in 2019 was 435 000/year, delaying ECG screening at around 60 days of age could lead to saving more than € 7 million per year. In fact, given the possibility of normal resting QTc even in patients with LQTS, in our study the ECG was repeated at 3 weeks' distance in every infant with prolonged QTc at first visit, with confirmed QTc normalisation in almost every patient. Even if the estimated incidence of LQTS is of 1/2000–3000 newborns, we evaluated 3467 infants and found only one true positive after three ECG tests, whose genetic test is still ongoing.

In addition, we believe that the timing of approximately 6 years of age, as proposed by Hayashi *et al*[9] for the first ECG screening would be too late since the peak of SIDS is between 2 and 6 months of life.[7] In fact, we must also consider that the incidence of LQTS is approximately 1/2000 newborns,[10] about 4 infants out of 10 000 die due to SIDS[21] and that 5%–10% of them have LQTS.[24] This is clear especially in the event of a newborn with LQTS, since an adequate and early treatment could not only prevent SIDS, but also overall premature arrhythmic deaths.[25 26] As a consequence, it could lead to a new diagnosis in older siblings or other family members, with high impact on possible morbidity and mortality.

Another interesting result is that in our study at 60 days of life, all QTc abnormalities found in neonates with positive family history disappeared. In this case too, our clinical choice would avoid repeated checks that would not be very useful but, at the same time, stressful and expensive for families.

CONCLUSION

ECG screening would be affordable for the national public health system if done at the right time of life, considering also the beneficial impact that it would have on public health. A possible limitation of our study is, unfortunately, the loss at follow-up of some patients with prolonged QTc. Further studies are warranted to confirm our initial result, also through a long-term follow-up.

Contributors AM and RL conceptualised and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. JL designed the data collection instruments and collected all data. MR conceptualised and designed the study, coordinated and supervised data collection, and performed all cardiology visits and ECG interpretations. RF and FV coordinated and supervised the statistical analysis and critically reviewed the manuscript for important intellectual content. MKF critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. CP reviewed the statistical analysis.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The study was conducted according to the World Medical Association Declaration of Helsinki. Given the retrospective nature of our study, Ethics Committee's approval was waived.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplemental information.

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