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Electrocardiographic Screening in the First Days of Life for Diagnosing Long QT Syndrome: Findings from a Birth Cohort Study in Germany

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Keywords
Sudden infant death · Electrocardiography screening · Long QT syndrome · Newborn · Birth cohort

Abstract
Introduction: Newborn sudden infant death syndrome (SIDS) has failed to decrease in the last decades, and a third of the neonatal cases occurred within the first 6 days of life. The long QT syndrome (LQTS) is a genetic disease with a prevalence of 1 in 2,000 live births and contributes to almost 10% of SIDS cases. Early identification of LQTS through electrocardiogram (ECG) screening is likely to reduce mortality. ***Methods and Results:*** In this ongoing prospective study we evaluated 2,251 ECGs from newborns participating in the KUNO Kids birth cohort study between July 2015 and July 2018. ECGs were recorded at a mean age of 2.0 days (IQR 0 days). The QT interval was corrected for heart rate using Bazett's formula (QTc). A QTc between 451 and 460, 461–470, and >470 ms was measured in 23 (1.0), 14 (0.6), and 62 (2.8%) participants, respectively. Fourteen neonates (0.62%) were admitted and monitored because their initial QTc was ≥500 ms. In 2 genetically analyzed participants, a mutation was found. One disease-causing for LQTS type 1 and the other of unclear significance. Cascade screening revealed affected members in both families. ***Conclusion:*** A standardized neonatal ECG screening in the first days of life is able to identify neonates with a relevant transient form of prolonged QT intervals and to aid diagnosing congenital LQTS.

Introduction

In infants, a severely prolonged QT interval is associated with life-threatening complications such as stillbirth, cardiac syncope, or sudden infant death syndrome (SIDS) [1–3]. It has been suggested that about 10% of all current SIDS cases could be explained by long QT syndrome (LQTS) [1, 2]. Effective treatment for LQTS is available, reducing the mortality from about 50% in symptomatic and untreated to under 2% in treated patients [4].

A prevalence of 1:2,000 LQTS is far more common than previously thought [5]. Broadly available genetic testing has vastly improved our knowledge of the underlying mutation and even made a genotype-specific management possible [6, 7]. An electrocardiogram (ECG)-

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guided genetic testing for LQTS is reported to be feasible, successful [5, 8], and cost-effective [9]. Additionally, every diagnosed case triggers a cascade of screening in family members, often leading to the identification of undiagnosed but affected relatives [10]. Therefore, LQTS meets several criteria that may make an ECG screening worthwhile [11].

Nevertheless, there are concerns about specificity and sensitivity as there is a high interobserver variability reported in interpreting ECGs [12, 13]. Especially, in newborns, ECG interpretation is challenging and difficult, as the QT interval varies with the progression of age and may change within days [14]. Thus, the major concern is the high number of primarily false-positive screening results an early screening might cause [13, 15]. Therefore, it was recommended not to conduct an ECG screening before the age of 3–4 weeks [1], and with a QTc cutoff of 460 ms in 2 different ECGs, the number of false positives is estimated to be low (~1 in 1,000) [11].

On the other hand, an early time point for diagnosis is desirable to prevent SIDS cases which are associated with LQTS [1, 2]. In Germany, basically every child is born in a hospital (97.13%) [16]. This is the time when every neonate can be clinically assessed, making it the ideal time point for an ECG recording from a logistic point of view. The purpose of this study was to investigate whether a very early ECG screening in the first week of life can be successfully implemented in clinical standard procedures after birth and be a valuable asset in diagnosing LQTS confirmed by genetic testing.

Methods

Study Population

We analyzed 2,251 ECGs that were recorded from participants of the KUNO Kids health study, which is a population-based prospective birth cohort study carried out at the Clinic St. Hedwig, Regensburg, Germany. The study methodology was already described elsewhere [17]. Eligible were all newborn babies born between July 27, 2015, and July 28, 2018. Exclusion criteria were outpatient childbirth, postpartal transfer of mother or child to an intensive care unit, stillbirth, maternal age <18 years, or maternal German language skills inadequate to achieve informed consent.

Electrocardiography

A first ECG was recorded in the first week of life in every participant. The recording and evaluation were executed according to standard operating procedures. The 12 lead ECG was performed with a commercially available recording device (MAC 5500 HD®; GE Healthcare, Freiburg, Germany) and 10 adhesive electrodes (Ambu® BlueSensor NF50-A/12; Ambu, Bad Nauheim, Germany) and recorded at a paper speed of 50 mm/s including an additional rhythm recording at 25 mm/s. All ECG records were evaluated or revised by experienced pediatric cardiologists (S.G. and H.M.). The QT interval was measured manually from the onset of the Q wave to the end of the T wave. The end of the T wave was defined as the intersection of a tangent to the steepest slope of the T wave and the baseline [18]. This method can lead to an underestimation of the QT interval if there is a double slope on the descending part of the T wave [19]. It was corrected for time (QTc) using Bazett's formula {QTc [ms] = QT interval [ms]/(√RR [s]/1[s])}, as recommended by the guidelines for interpretation of neonatal ECG of the European Society of Cardiology [20, 21]. If in our study QTc was prolonged (>450 ms) or borderline (440–449 ms) in a single measurement in lead II, we calculated a mean value according to Schwartz et al. [5].

Control ECG Recording

Based on recommendations by Saul et al. [11] every newborn with a mean QTc over 450 ms in their initial ECG received a control recording before discharge and/or after 3–4 weeks. If QT prolongation (>450 ms) was confirmed or any other ECG abnormality was identified (e.g., bradycardia, arrhythmia), the infants were managed and treated according to the appropriate guidelines [20]. Participants showing an exceedingly prolonged QTc interval of ≥500 ms were admitted to neonatology and monitored continuously.

Genetic Testing

Genetic testing was performed in participants with repeatedly prolonged QT intervals or other pathological findings that merited a genetical evaluation (e.g., profound sinus bradycardia, ventricular ectopic beats). An additional consent for the analysis was obtained in every case.

Statistical Analysis

All ECG parameters with relevance to these analyses (QTc, heart rate, etc.) were entered in an electronic case report form and extensive plausibility checks were performed. We calculated descriptive statistics. Frequencies and percentages are reported for dichotomous and categorical variables and means and standard deviations (SD) for metric variables, respectively. All analyses were computed using IBM SPSS statistics (version 23).

Results

Between July 27, 2015, and July 28, 2018, a total of 2,684 participants were enrolled in the KUNO Kids birth cohort study. Of those, 49.1% were female. The participants were born after a mean duration of pregnancy of 39.5 weeks (SD 1.6 weeks) with a mean weight of 3,352 g (SD 507 g) and a mean length of 51 cm (SD 2.6 cm). Most participating families hold German nationality (89.7%) [17].

Of these, 433 were excluded because of missing consent for clinical examination or an ECG recorded after the eighth day of life. The ECGs of 2,251 participants were

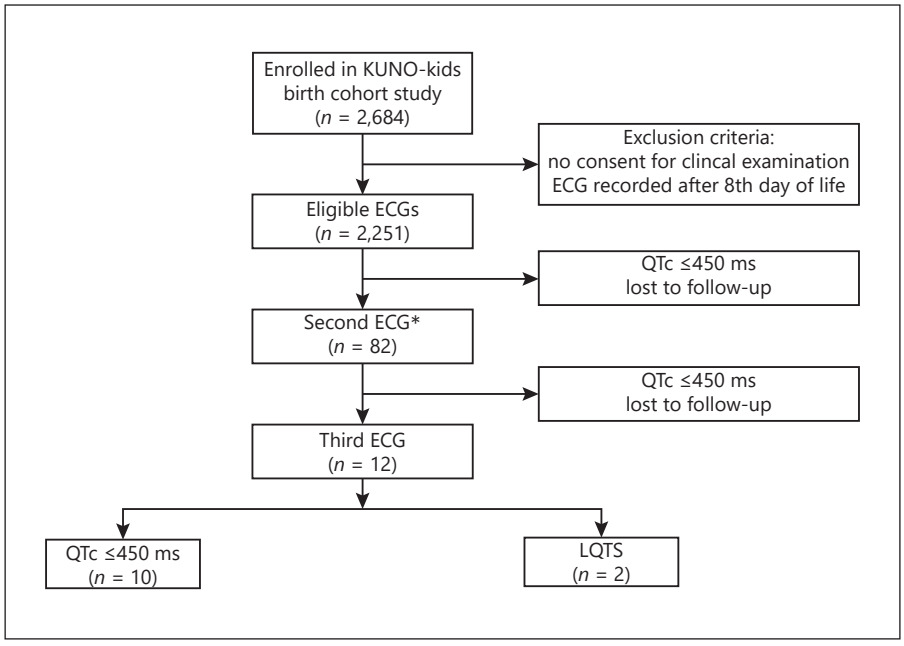

Fig. 1. Study population and results of the ECG screening for LQTS. This flowchart shows the population of the KUNO Kids birth cohort study and the number of participants included in this study. The first ECGs were recorded at a mean age of 2 days (SD 0.8 days, IQR 0 days). For the number of second and third ECGs we only show participants who had a prolonged QTc of >450 ms in their first ECG. These were recorded at a mean age of 19.1 days (SD 25.7 days, IQR 27 days) and 57.5 days (SD 64.4 days, IQR 80 days) respectively. From 12 participants who received 3 ECGs we genetically confirmed 2 diagnoses of LQTS. *A second ECG was recommended for 99 (4.40%) participants with prolonged QTc and for 80 (3.55%) participants with nonmeasurable QT intervals. From these 179 (7.95%), only 131 showed up for their second ECG. The rest were lost to follow-up. ECG, electrocardiogram; LQTS, long QT syndrome; SD, standard deviation.

evaluated (Fig. 1). These ECGs were recorded at a mean age of 2.0 days (SD 0.8 days, IQR 0 days, Q1 2 days, Q3 2 days) with a mean heart rate of 117 bpm (SD 17 bpm, IQR 22 bpm) and a mean QTc of 414 ms (SD 25, IQR 28 ms). From these ECGs, 2,072 (92%) showed normal QTc <450 ms, 99 (4.4%) showed a prolonged QTc of >450 ms, and in 80 (3.6%), the QT interval was not measurable because of artifacts, nondistinguishable T waves, or recording errors.

Participants with Prolonged QTc >450 ms

In 99 out of 2,251 participants (4.4%), the initial QTc interval was prolonged (>450 ms) with a mean QTc of 482 (SD 24 ms, IQR 35 ms) (Table 1). Forty-two of these participants were female showing a mean QTc prolongation of 479 ms (SD 24 ms) and 57 male participants showing a mean QTc of 484 (SD 24 ms), respectively. In 23 participants the ECG showed a slight QTc prolongation of 451–460 ms; in 14:00, a moderate QTc prolongation of 461–470 ms; and in 62 participants, a prolonged QTc interval of over 470 ms was present.

Of 99 participants with prolonged QTc >450 ms, 82 received a second ECG and 17 were lost to follow-up. These ECGs were recorded at a mean age of 19.1 days (SD 25.7 days, IQR 26.8 days). In these second ECG recordings, the QTc declined from a mean of 482 ms (SD 24 ms; IQR 35 ms, $n = 99$) to a mean of 426 ms (SD 27 ms; IQR 43 ms, $n = 78$), with a mean decline of 56 ms (SD 31 ms) per participant (Fig. 2). In the second ECGs of 4 participants, the QT interval was not measurable.

From those with an extensive prolongated QTc interval in the first ECG, 11 out of 62 showed a prolongation in their control as well and 41 a normalized QTc of <450 ms. In the group of moderately prolonged QTc intervals, 1 participant out of 14 showed a QTc >450 ms in the control recording and none from the slightly prolonged.

Table 1. Comparison of the distribution of QTc intervals in different populations of infants

QTc (ms)	Italian population [7] $n = 43,080$	Japanese population [11] $n = 4,285$	KUNO Kids population $n = 2,251$
Age at screening	2–4 weeks	4 weeks	First week of life
>470	31 (0.07%)	5 (0.12%)	62 (2.8%)
461–470	28 (0.06%)	3 (0.07%)	14 (0.6%)
451–460	177 (0.41%)	34 (0.79%)	23 (1.0%)
440–450	858 (2.00%)	172 (4.01%)	51 (2.3%)
LQTS diagnoses	17 (0.04%)	1 (0.02%)	2 (0.09%)

Depicted are the results from 3 studies from Italy [7], Japan [11], and Germany respectively. Compared are the prevalence of LQTS and the distribution of QTc intervals in the different ECG screening programs. LQTS, long QT syndrome, ECG, electrocardiogram.

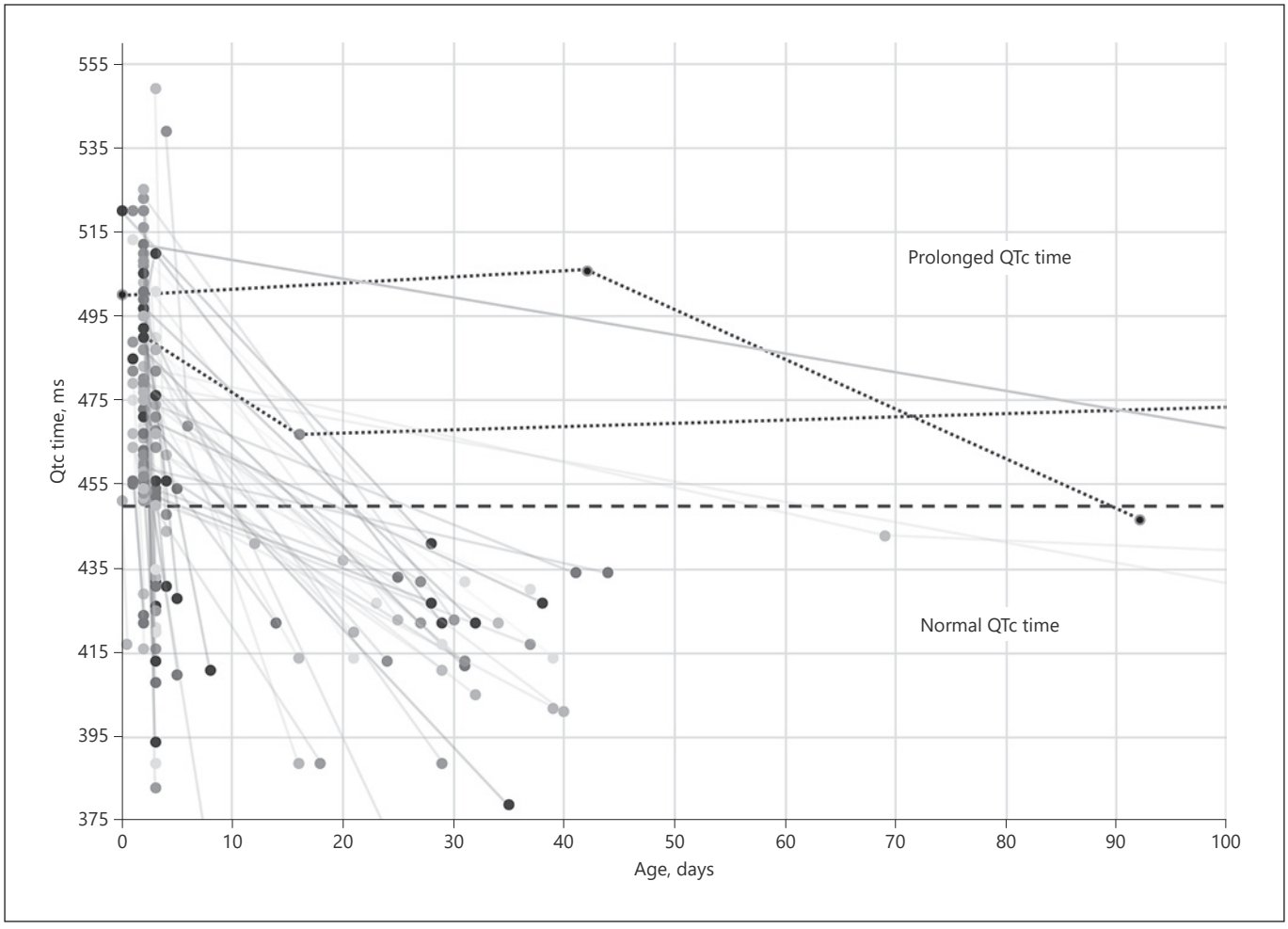

Fig. 2. Depicted are the QTc values from 99 participants with a prolonged QTc time of over 450 ms (dashed line) in their initial ECG. QTc values are shown until they become "normal" (≤450 ms). For the purpose of this figure the continuation of this graph is interrupted at the hundredth day of life, although we recorded ECGs later. Highlighted are the 2 participants with genetically confirmed LQTS (dotted lines). ECG, electrocardiogram; LQTS, long QT syndrome.

A total of 12 participants received a third ECG because of a prolonged QTc >450 ms. These ECGs were recorded at a mean age of 57.5 days (SD 64.4 days, IQR 66 days). One participant showed a QTc interval of 481 ms (Fig. 3) and has been referred for genetic testing. A disease-causing mutation for LQTS type 1 was discovered (NM_000218.2:c.824_826delTCT, p. [Phe257del], Exon 6. KCNQ1), and therapy with a beta blocking agent (propranolol) was started.

Fourteen neonates (0.62%) were admitted to the neonatal ward because their initial QTc was extensively prolonged (≥500 ms). One of them, with a prolonged QTc interval of 506 ms showed frequent ventricular ectopic beats on a 24-h Holter monitoring during inpatient care. In this participant genetic analysis was performed and propranolol therapy was initiated despite a normalized QTc interval in the third ECG. This infant showed a mutation in the KCNQ1 gene with a reduced functional penetrance for LQTS (c.217C>A [p.Pro73Thr, KCNQ1-Gene]) (Fig. 3).

Cascade Screening

In both participants with confirmed mutation in the KCNQ1 gene a genetic counseling of the family was recommended. In the family of the first participant the mother was affected by the same mutation. She did not show any symptoms at this time but described episodes of syncope in her youth. Furthermore, she showed a QTc

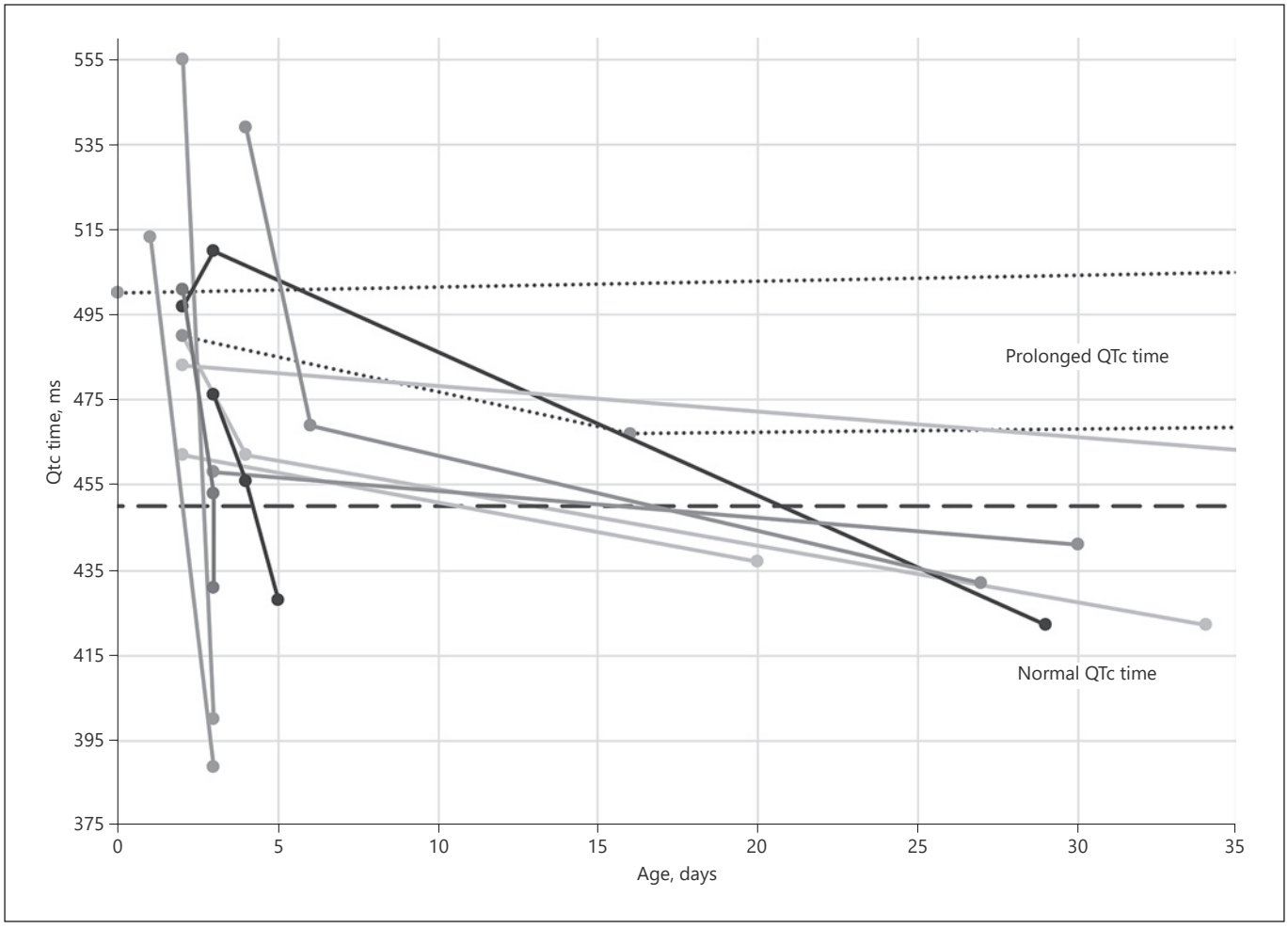

Fig. 3. This figure shows a section of Fig. 2. Depicted are the QTc values of the 12 participants with a primarily prolonged QTc time of over 450 ms (dashed line) who received at least 3 ECGs. For a better overview the continuation of this graph is interrupted at the thirty-fifth day of life, although we also recorded ECGs later. Highlighted are the 2 participants with genetically confirmed LQTS (dotted lines). ECG, electrocardiogram; LQTS, long QT syndrome.

of 468 ms in her ECG recording. The first and the second sibling of this participant also showed a significant prolongation of the QTc interval (>500 ms) on the first day of life (age 2 and 4 h respectively) and treatment with a beta blocking agent (propranolol) was initiated promptly. In both siblings, diagnosis was confirmed genetically, showing the same mutation. In the family of the second participant the same mutation was found in the father and his brother. Neither man presented any symptoms or a QTc prolongation in their ECG recordings (QTc <440 ms).

Discussion

This prospective cohort study shows that a standardized neonatal ECG screening in the first days of life is able to identify neonates with a relevant transient form of prolonged QT intervals and to aid the diagnosis of congenital LQTS as confirmed by genetic testing. Two out of 2,251 participants from our study population were diagnosed with a mutation in the KCNQ1 gene. In both infants a treatment with a beta blocking agent (propranolol) was started and genetic counseling of the family was recommended.

Our study population showed QTc intervals of over 470 ms in 2.8% of newborns, compared to 0.7 and 0.12% reported previously in neonates at the end of the first

month of life (Table 1). These prolonged QT intervals measured shortly after birth decreased impressively and normalized within days (Fig. 2). It must be mentioned that values <460 ms are still very close to normal.

It is well known that the QTc interval varies with age, especially in the early neonatal period [22]. Why in some children QT intervals are extensively prolonged and then show rapid normalization is not totally clear yet. Potentially, these children are exposed to factors perinatally or even prenatally that prolong QT intervals, such as maternal antiarrhythmic or antibiotic therapy, maternal connective tissue diseases, delivery mode, or a positive family history regarding LQTS [23].

It is important to highlight that as long as the QT interval remains high above normal values these neonates might have a transient elevation of risk for ventricular tachycardia irrespective of a diagnosis of LQTS [24]. In 14 participants (0.62%) of our study cohort the initial QTc interval was ≥500 ms and therefore they were admitted to the neonatal ward. One participant presented with frequent ventricular ectopic beats during inpatient care and was diagnosed with a mutation of uncertain significance in KCNQ1. None of the other admitted participants experienced hypoxia or relevant arrhythmias and the QT interval fortunately became normal.

Schwartz et al. [1] described that a prolonged QT interval in the first week of life is strongly associated with SIDS. Since the incidence of SIDS peaks between the first and the fourth month of life, there is a considerable amount of SIDS cases in the neonatal period (<26 days) [25, 26]. Therefore, even when keeping in mind that there is a regression to normal QT intervals in most children, there is good reason to propagate ECG screening to take place as early as possible and feasible in life. At this point, ECG is also superior to genetic testing as a first screening tool, as there is no genetic test which captures all different forms of LQTS and other arrhythmias. Rather, genetic testing should be applied as a second step in those that show abnormal ECG results.

Furthermore, there are concerns regarding the psychological long-term effects a false-positive screening result would have on the patients and their family. These questions need to be properly addressed, before advocating a screening can be considered.

The conducted cascade screening lead to the diagnosis of affected individuals in the families of both participants with confirmed mutation in the KCNQ1 gene. The family of the first participant is clearly affected by LQTS and went undetected so far. The identification of the mutation was of huge significance for this family. In the second family the mutation is described as of unclear significance. After consulting with experts, we decided to initiate treatment with a beta blocking agent in the participant for the first years of life [27]. This is important as these findings show that a cascade screening of family members can identify affected individuals and may therefore prevent sudden cardiac events [10].

Limitations

With the number of children studied in the KUNO Kids birth cohort study so far, we cannot determine prevalence of LQTS for the studied population. Furthermore, our results cannot be used to assess true LQTS prevalence in the German population because of its single-centered approach and the exclusion of families with inadequate German language skills.

It needs to be stated that not all individuals affected by congenital LQTS show a permanent prolongation of QTc intervals [13]. Therefore, it is possible that we may have missed individuals with a congenital LQTS with our screening method. With the long-term follow-up design of the KUNO Kids study spanning at least 18 years, we try to identify false-negative screening results.

The approach to perform these ECG recordings in the first week of life yields a higher number of prolonged, unmeasurable, and even severely prolonged QT intervals than studies performed around the age of 1 month (Table 1) [5, 8]. This leads to a higher number of initial false-positive results and furthermore, to a higher proportion of control ECGs. Furthermore, most of the initially prolonged or even severely prolonged QT intervals normalized within a short period of time. Regarding these important aspects an ECG screening conducted later in the neonatal period would yield results more precise and showed to be cost-effective [9]. Despite these facts an ECG screening in infancy has not yet been implemented in any European country. Therefore, this study gives important insight to a "second best" approach.

A further limitation of this study is the fact that a significant number of participants were lost to follow-up. This represents the reality in clinical practice, as parents decided not to show up to follow-up appointments. For a screening program this would not be acceptable and shows the need of a well-structured follow-up program.

We did not perform an analysis of interobserver variability. So long as there is no validated automated ECG analysis the interpretation of ECGs is heavily depended on the expertise of the investigator. Future participants of

the KUNO Kids birth cohort study with an initial QTc of ≥500 ms will be referred to genetic counseling, if there are no known confounding factors causing transient QTc prolongation (e.g., maternal medication).

Conclusion

Taken together, our data shows that ECG screening in the first days of life is able to identify neonates with a relevant transient form of a prolonged QT interval and to aid diagnosing congenital LQTS. This early approach yields a higher number of initial false-positive results. A screening in the fourth week may entail results more precise but has not been implemented in European countries so far. Rather, this approach needs to be seriously considered, as it enables a straightforward access to a majority of the newborn population.

Such an early screening of asymptomatic neonates is also justified by the fact that most of those affected by LQTS who die, do so without previous symptoms [20, 28]. With an effective and even mutation-specific management of LQTS it seems possible to prevent a relevant part of cardiac events from very early on [7].

Statement of Ethics

Participation was voluntary and written informed consent was obtained for each case. The study was approved by the Ethics Committee of the University of Regensburg (14-101-0347)

Conflict of Interest Statement

All authors declare that they have no competing financial or personal interests.

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Author Contributions

Study design: M.K. and S.G. Data collection: A.S., S.G., M.K., A.S., A.P., M.M., B.S.G., and H.M. Statistical analysis and data interpretation: A.S., S.G., S.B., and M.K. Manuscript writing: A.S., S.G., and M.K.

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