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## Article

# Early Screening for Long QT Syndrome and Cardiac Anomalies in Infants: A Comprehensive Study

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**Abstract:** (1) Background: Sudden Infant Death Syndrome (SIDS) represents unexplained and sudden deaths during the sleep of infants under one year of age, despite thorough investigation. Screening for prolonged QTc or Long QT Syndrome (LQTS) should be conducted on all newborns to reduce the incidence of SIDS. Neonatal electrocardiogram (ECG) could identify congenital heart defects (CHD) early, especially those not detected at birth. Infants with prolonged QT intervals typically undergo genetic analysis for Long QT Syndrome; (2) Methods: The study involved infants aged 20-40 days, born clinically healthy, with initial ECG screening. Infants with prenatal diagnoses or signs/symptoms of CHD identified immediately after birth, as well as those who underwent ECG or echocardiogram for other clinical or historical indications, were excluded from the study. The data were analyzed using SPSS version 22.0; (3) Results: Of the 42,200 infants involved, 2,245 were enrolled, with 39.9% being males. Subsequently, 164 children (37.8% males) with prolonged QT intervals underwent further diagnostic investigations. Genetic mutations were identified in 11 out of 18 tested children. The most common mutations were LQT1 (54.5%), LQT2 (36.4%), and LQT3 (1 patient). Medications used included propranolol (39.8%), nadolol (22.2%), inderal (11.1%), metoprolol (11.1%), and no treatment (16.7%). The most common abnormalities were focal right bundle branch block (54.5%), left axis deviation (9.2%), and nonspecific ventricular repolarization abnormalities (7.1%). Multiple anomalies were found in 0.47% of children with focal right bundle branch block. Structural abnormalities were associated with specific features in 267 patients (11.9%), primarily isolated patent foramen ovale (PFO) at 61.4%; (4) Conclusions: The screening has proven effective in early diagnosing Long QT Syndrome and other cardiac rhythm anomalies, with additional benefits in detecting mutations and/or QTc prolongations in family members. Identifying other ECG abnormalities and congenital heart malformations further enhances the benefits of the screening.

**Keywords:** children; congenital heart disease; Electrocardiogram; Infant; long QT syndrome; neonatal screening; sudden infant death syndrome

## 1. Introduction

The term SIDS (sudden infant death syndrome) refers to the seemingly unexplained and sudden death during sleep of an infant under one year old after a thorough and careful investigation [1]. SIDS still stands as the leading cause of death in the first year of life in Western countries [2]. In 1995, the syndrome was documented at 5.6 cases per 10,000 births [3], varying between 2 and 5 per 10,000 live births in most countries [4]. A noteworthy observation is that fifty percent of deaths occur between 7.6 and 17.6 weeks from birth [3] [2].

The cause of sudden death in some infants has long been theorized as multifactorial, involving interactions among various factors. These factors lead to death if expressed or experienced in combination with one or more others [5]. The primary exogenous risk factors include the prone sleeping position [6] [7] [8], exposure to cigarette smoke [9] [10], bed-sharing [11], sleeping on soft

surfaces [12], and covering the baby's head under the sheets [13]. Among the various protective factors are breastfeeding [14], pacifier use [15], and placing the crib in the same room as the parents [2].

Possible endogenous causes may encompass systemic anomalies, neurological or autonomic dysfunctions [16], prematurity [3], and pregnancy-related factors [17]. In numerous SIDS cases, immune system activation [7] and down-regulation of the anti-inflammatory pathway have been noted, rendering the infant more susceptible to infections [18]. Metabolic disorders appear to account for 2% of SIDS cases [19] [7].

Neonatal arrhythmias are categorized as either benign or non-benign. Non-benign arrhythmias include supraventricular tachycardia (SVT), ventricular tachycardia (VT), abnormalities in atrioventricular (AV) conduction, and genetic arrhythmias such as congenital long QT syndrome (LQTS) [20].

Specific genes have been linked to the development of arrhythmias that may be responsible for sudden infant death syndrome (SIDS) [21]. Notably, cardiac channelopathies are of significant concern [8]. Approximately 10% of SIDS cases have been attributed to cardiac channelopathies [8]. The scrutiny of all genes associated with SIDS underscores the importance of routine post-mortem genetic screening in suspected cases of SIDS, mainly focusing on genes related to cardiac arrhythmias [22]. This screening facilitates the identification of the most likely cause of death and identifies family members at risk [23].

A molecular association between long QT syndrome and SIDS has been documented [24]. According to the 2015 ESC guidelines [25], long QT syndrome is diagnosed when QTc  $\geq$  480 msec in repeated 12-lead ECGs or the Risk score for LQTS is  $> 3$ . Schwartz et al. found that infants who succumbed to SIDS exhibited a prolonged corrected QT interval (QTc) in comparison to survivors ( $435 \pm 45$  vs.  $400 \pm 20$  msec,  $P < 0.01$ ) and infants who died from causes other than SIDS ( $393 \pm 24$  msec,  $P < 0.05$ ) [26]. In 9.5% of SIDS cases, functionally significant genetic variants in Long QT Syndrome (LQTS) genes were identified [27]. LQTS is analyzed in the presence of a confirmed pathogenic mutation, irrespective of the duration of QTc [28]. Specifically, mutations in 14 genes encoding channels responsible for long QT syndrome have been recognized [29]. Roughly 75% of clinically defined LQTS cases result from mutations in three genes: KCNQ1 (LQT1), KCNH2 (LQT2), and SCN5A (LQT3) [30]. However, there is currently no comprehensive genetic test to identify infants at risk of SIDS, and the field is still grappling with methodological challenges [31].

Infants with inherited arrhythmias (ventricular tachycardia or fibrillation, long QT syndrome, or high-grade atrioventricular block) may face an elevated risk of congenital heart defects (CHD) [32]. CHD stands out as the most diagnosed genetic disorder in newborns. The prevalence of CHD at birth exhibits temporal and global variations. In Europe, the reported prevalence of CHD was 8.2 cases per 1,000 live births [95% CI: 8.1 to 8.3] [33]. The incidence of CHD has shown stability over the past three decades, indicating limited advancements in CHD prevention strategies [34].

Arrhythmogenic cardiomyopathy (ACM) represents a distinct hereditary form of cardiomyopathy characterized by prominent ventricular arrhythmias and often associated with sudden cardiac arrest. Conventional estimates of ACM typically suggest that between 1 in 2,000 and 1 in 5,000 people are affected [35].

To mitigate the incidence of SIDS, screening for prolonged QTc or Long QT Syndrome (LQTS) must possess sufficient sensitivity and be administered to all newborns [36]. Furthermore, the use of neonatal electrocardiogram (ECG) could aid in early identification of congenital heart defects (CHD), particularly those that may be undisclosed at birth [37] [38].

### *Aims of the study*

This study aims to evaluate whether an electrocardiogram (ECG) conducted in the neonatal period can significantly contribute to the early identification of children at risk of cardiovascular mortality and morbidity, encompassing arrhythmias, Long QT Syndrome (LQTS), and congenital heart defects (CHD) that may be undisclosed at birth.

## 2. Materials and Methods

### *Patients' enrolment*

This retrospective study was carried out at the Sleep-Related Respiratory Disorders clinic for ALTE/BRUE and SIDS at the University of Insubria and the Pediatric Cardiology Department of the Filippo Del Ponte Hospital in Varese, Italy.

All healthy infants underwent an ECG screening test primarily to investigate Long QT Syndrome (LQTS). Infants with prolonged QT intervals underwent follow-up and analysis for genetic mutations associated with Long QT Syndrome. The study aimed to identify other congenital heart defects (CHD) that may have gone unrecognized at birth.

The study included infants between 20 and 40 days who were born clinically healthy and had undergone initial routine ECG screening. Infants with prenatal diagnoses or signs/symptoms of CHD identified immediately after birth, as well as those who underwent ECG or echocardiogram for other clinical or historical indications, were excluded from the study.

### *Electrocardiographic screening*

Analyzing paper medical records allowed us to identify infants with a prolongation of the QT interval observed in the first and/or subsequent ECG tracings taken at one- or two-week intervals. Twelve-lead ECGs were recorded on millimeter paper at 25 mm/sec speed using a Philips PageWriter TC50 electrocardiograph. Pediatric cardiologists manually analyzed the ECG tracings, following the European Society Guidelines for interpreting neonatal ECG [39]. QTc was considered prolonged when the QT interval, calculated with the Bazett formula, was  $\geq 435$  msec, rounding it up [40].

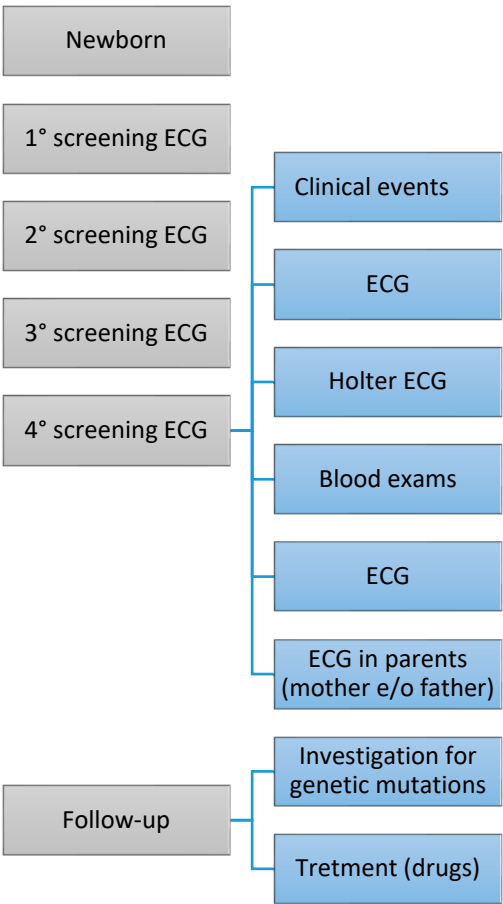
Children with prolonged QTc ( $\geq 435$  msec) confirmed in multiple consecutive tracings (between three and four ECGs) were then subjected to a more in-depth screening.

### *Laboratory and instrumental tests*

In some children, the following investigations were conducted to rule out the secondary causes of QT interval modification: blood tests, Holter ECG, and 12-lead ECG on family members (mainly the mother and/or father). Additionally, selected children underwent an echocardiogram to identify congenital heart defects not previously recognized. Specifically, infants with persistent prolongation of the QTc interval were evaluated for the possible onset of symptoms related to Long QT Syndrome, the results of the Holter ECG, and a therapeutic approach.

### *Genetic Testing*

Genetic testing was performed using next-generation sequencing (NGS) to identify any of the pathogenic mutations in Long QT Syndrome (KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, and KCNJ2) associated with SIDS and the patient's family members. [22].



**Figure 1.** The figure comprises a series of phases that unfold over time. The frequency of examinations may vary based on the severity of the congenital heart defect (CHD). The treatment for CHD can differ depending on the type of cardiac condition.

*Statistical analysis*

The data were recorded in a Microsoft® Excel® database for Windows 11 and statistically analyzed using SPSS version 22.0 for Windows (SPSS Inc., Chicago, IL). Categorical variables are presented as each category's number (n) and percentage (%) of observations.

Continuous variables are reported with mean, standard deviation (SD), minimum, and maximum values. Group characteristics are expressed as mean, SD, standard error (SE), 95% confidence interval (95% C.I.), minimum value (Min), and maximum value (Max) for the variables of interest.

The Mann-Whitney U test was conducted to identify statistically significant differences between study groups.

**3. Results**

This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

*Electrocardiographic screening*

The study involved 42,200 infants (82.4% of those born from 2002 to 2017).

Table 1A presents the percentage of children with QTc values ≥ a predefined cut-off (msc) according to four different follow-up ECGs (ECG 1.0, ECG 2.0, ECG 3.0, and ECG 4.0), along with the percentage of males in each category. The baseline enrollees were 2,245 children (39.9% males).



**Table 1. A.** Table 1 displays the percentage of children (percentage of males). Initially, 2,245 children were assessed (39.9% males). In subsequent control ECGs (from the 1st ECG to the 4th ECG), they exhibited prolonged QTc. Among these, 164 children were recruited (37.8% males) and underwent further diagnostic investigation. Data related to the ECGs, from the 1st repeat ECG to the 4th repeat ECG, are presented.

Included at follow-up, QTc (mcs)	ECG 1.0, n. (%) males)	ECG 2.0, n. (%) males)	ECG 3.0, n. (%) males)	ECG 4.0, n. (%) males)	ECG 1.1, n. (%) males)	ECG 2.1, n. (%) males)	ECG 3.1, n. (%) males)	ECG 4.1, n. (%) males)	Holter 24-hour ECG, no. (% males)
Arruolati al t0	2,245 (39.9)	667 (35.2)	254 (29.1)	52 (25)	164 (37.8)	119 (32.8)	87 (24.1)	23 (26.1)	44 (31.8)
	% (%) males)	% (%) males)	% (%) males)	% (%) males)	% (%) males)	% (%) males)	% (%) males)	% (%) males)	% (%) males)
≥ 435	98.8 (38.9)	99.3 (35.2)	95.7 (58.9)	55.8 (24.1)	99.4 (37.4)	72.6 (32.8)	100 (24.1)	100 (26.1)	100 (30.2)
≥ 440	86.8 (39.8)	88.0 (34.2)	89.4 (27.3)	92.3 (27.1)	89.0 (37.0)	64.6 (32.1)	92.0 (23.8)	91.3 (28.6)	95.5 (25.6)
≥ 445	37.8 (37.6)	46.0 (27.4)	59.8 (24.3)	57.7 (13.3)	53.0 (32.2)	40.2 (24.2)	62.1 (22.2)	60.9 (14.3)	95.5 (31.0)
≥ 450	33.4 (37.8)	42.3 (26.2)	55.9 (25.4)	53.8 (14.3)	48.2 (32.9)	38.4 (25.4)	58.6 (23.5)	56.2 (14.4)	86.4 (23.2)
≥ 455	14.7 (34.5)	22.8 (22.4)	26.8 (26.5)	34.6 (11.1)	26.8 (29.5)	26.2 (23.3)	26.4 (26.1)	39.1 (11.1)	68.2 (26.7)
≥ 460	9.6 (30.6)	13.2 (14.8)	17.3 (29.5)	19.2 (20.0)	20.1 (30.3)	16.5 (18.4)	14.9 (30.8)	21.7 (20)	59.1 (15.9)
≥ 465	4.9 (33.3)	8.6 (8.3)	8.7 (18.2)	11.5 (33.3)	12.8 (42.9)	7.3 (16.7)	4.6 (0)	13.0 (33.3)	45.5 (25.0)
≥ 470	3.6 (34.6)	5.4 (5.6)	5.4 (0)	3.8 (0)	7.9 (38.5)	7.3 (16.7)	4.6 (0)	4.3 (0)	29.5 (7.9)
≥ 475	0.67 (26.7)	2.4 (6.3)	3.5 (0)	3.8 (0)	2.4 (25)	3.7 (16.7)	3.4 (0)	4.3 (0)	22.7 (20.0)
≥ 480	0.49 (36.4)	2.4 (6.3)	3.5 (0)	3.8 (0)	1.8 (33.3)	3.7 (16.7)	3.4 (0)	4.3 (0)	20.5 (5.5)
≥ 485	0.22 (20)	2.1 (7.1)	2.0 (0)		0.61 (0)	3.0 (20)	1.1 (0)		18.2 (25.0)
≥ 490	0.22 (20)	1.6 (9.1)	2.5 (0)		0.61 (0)	2.4 (25)	1.1 (0)		15.9 (4.3)
≥ 495	0.22 (0)	1.3 (0)	1.2 (0)		0.61 (0)	1.8 (0)	1.1 (0)		11.4 (20.0)
≥ 500	0.22 (0)	1.3 (0)	1.2 (0)						9.1 (2.4)
≥ 510	0.22 (0)	0.9 (0)	1.2 (0)						4.5 (1.2)

100-80%	80-60%	60-40%	40-20%	20-0%
100-80%	80-60%	60-40%	40-20%	20-0%
100-80%	80-60%	60-40%	40-20%	20-0%

Legend: ECG, electrocardiogram; S.D., standard deviation.

For instance, at the ECG 1.0 follow-up, 37.8% (37.6%) of the subjects had a QTc ≥ 445 mcs, while at the ECG 4.0, this percentage had increased to 57.7% (13.3% males). Furthermore, Table 1A displays the same results regarding QTc values at the follow-up of children who were subsequently enrolled for advanced monitoring. These selective ECGs are denoted as ECG 1.1, ECG 2.1, ECG 3.1, and ECG 4.1. Specifically, the number of subjects enrolled at baseline was 164 (males 37.8%). At ECG 1.1, 53.0% (32.2% males) of the subjects had a QTc ≥ 445, while at the fourth follow-up ECG 4.1, this percentage had increased to 60.9% (14.3% males).

Finally, Table 1A presents the QTc values from the Holter ECG. The number of subjects enrolled at baseline was 44 (31.8% males). Notably, the percentage of subjects with QTc ≥ 445 on the Holter ECG was 95.5% (31% males), while for QTc ≥ 455 on the Holter ECG, it was 68.2% (26.7% males).

**Table 1. B.** Table 1B displays milliseconds' mean QTc values ± S.D. (min-max). Initially, 2,245 children were assessed (39.9% males). In subsequent follow-up ECGs, from ECG 1.0 to ECG 4.0, they exhibited prolonged QTc. Among these, 164 children were selected (37.8% males) and were then subjected to further diagnostic investigation.

Included at follow-up (QTc, mcs)	ECG 1.0, QTc mean ± S.D.	ECG 2.0, QTc mean ± S.D.	ECG 3.0, QTc mean ± S.D.	ECG 4.0, QTc mean ± S.D.	ECG 1.1, QTc mean ± S.D.	ECG 2.1, QTc mean ± S.D.	ECG 3.1, QTc mean ± S.D.	ECG 4.1, QTc mean ± S.D.	Holter 24-hour ECG, mean QTc ± S.D. (min-max) mcs
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	(min-max) mcs	(min-max) mcs	(min-max) mcs	(min-max) mcs	(min-max) mcs	(min-max) mcs	(min-max) mcs	(min-max) mcs
Arruolati al t0	445.9 ± 9.4 (392-513)	448.1 ± 12.1 (427-513)	450.2 ± 12.7 (428-520)	450.5 ± 11.2 (435-482)	449.6 ± 11.9 (433-513)	451.7 ± 14.8 (435-513)	450.4 ± 12.1 (435-520)	451.3 ± 11.6 (435-482)
≥ 435	446.1 ± 9.2	448.3 ± 12.1	450.3 ± 12.6	449.9 ± 10.9	449.7 ± 11.9	451.7 ± 14.8	450.4 ± 12.1	451.3 ± 11.6
≥ 440	447.5 ± 9.0	449.8 ± 11.9	452.0 ± 12.2	451.8 ± 10.6	451.3 ± 11.5	453.6 ± 14.6	451.7 ± 11.7	452.9 ± 11.0
≥ 445	455.2 ± 8.7	457.5 ± 12.1	457.0 ± 12.0	458.0 ± 8.7	457.9 ± 10.7	460.9 ± 14.1	456.3 ± 11.7	458.5 ± 9.0
≥ 450	456.3 ± 8.6	458.4 ± 12.2)	457.7 ± 12.2	458.8 ± 8.5	459.0 ± 10.6	461.5 ± 14.1	456.9 ± 11.8	459.4 ± 8.7
≥ 455	463.7 ± 8.3	465.2 ± 13.3	465.6 ± 13.7	463.1 ± 7.6	465.8 ± 9.8	466.7 ± 14.4	464.7 ± 14.1	463.1 ± 7.8
≥ 460	467.0 ± 8.6	470.8 ± 15.1	470 ± 15.4	457.2 ± 8.2	468.5 ± 10.0	472.5 ± 15.7	470.4 ± 16.9	467.2 ± 8.7
≥ 465	472.6 ± 8.9	479.2 ± 16.2	479.3 ± 17.4	471.3 ± 8.3	472.7 ± 10.3	484.7 ± 16.5	489.5 ± 20.7	(466-482)
≥ 470	475.0 ± 9.3	483.7 ± 16.4	488.5 ± 17.4	482	476.9 ± 11.3	484.7 ± 16.5	489.5 ± 20.7	482
≥ 475	488.4 ± 15.7	499.1 ± 13.3	495.4 ± 16.7	482	487.3 ± 17.3	497.5 ± 14.2	(482-520)	482
≥ 480	492.9 ± 16.2	499.1 ± 13.3	495.4 ± 16.7	482	513	497.5 ± 14.2	520	482
≥ 485	508.4 ± 10.3	501 ± 11.8	506 ± 15.2		513	501 ± 12.7	520	499.5 ± 8.8
≥ 490	508.4 ± 10.3	506.4 ± 8.6	506 ± 15.2		513	505 ± 10.4	520	501.6 ± 7.1
≥ 495	513	510 ± 3.1	(511-520)		513	(506-513)	520	504.6 ± 5.9
≥ 500	513	510 ± 3.1	(511-520)					506.0 ± 5.8
≥ 510	513	512.0 ± 1.1	(511-520)					511

Legend: ECG, electrocardiogram; S.D., standard deviation.

Table 1B presents the mean values ± S.D. of QTc ranging from 435 mcs to 513 mcs (in increments of 5 mcs) during the four follow-up ECGs (ECG 1.0, ECG 2.0, ECG 3.0, and ECG 4.0). For instance, at the ECG 1.0 follow-up, the mean value ± S.D. for children with QTc ≥ 445 mcs was 455.2 ± 8.7 mcs, while at ECG 4.0, it was 458.0 ± 8.7 mcs. Additionally, Table 1B displays results related to QTc values for children enrolled for further diagnostic investigation (ECG 1.1 follow-up, ECG 2.1 follow-up, ECG 3.1 follow-up, and ECG 4.1). The mean value ± S.D. for subjects with QTc ≥ 445 mcs enrolled at baseline (t0) was 457.9 ± 10.7 mcs at ECG 1.1 and 458.5 ± 9.0 mcs at ECG 4.1. Finally, the table shows the mean values ± S.D. of QTc measured with Holter ECG ≥ 445 mcs as 467.2 ± 18.3 mcs

Genetic investigation

**Table 2.** The QTc values from follow-up ECGs 1.1 to 4.1 and the QTc obtained from Holter ECG in 27 children (18.5% males) undergoing further diagnostic investigation are as follows.

	N	Mean ± SD	Minimum – maximum
ECG 1.1 QTc msec	27	452,5 ±13,1	435 – 476
ECG 2.1 QTc msec	25	458,5 ±19,1	435 – 511
ECG 3,1 QTc msec	21	462,2 ±20,9	441 – 520
ECG 4.1 QTc msec	12	457,0 ±11,2	442 – 482
ECG Holter, QTc msec	18	452,9 ±26,2	417 – 538

Of the 27 children enrolled for further diagnostic investigation, 18 underwent genetic testing. Among the 18 children genetically examined, mutations were identified in 11, while no mutations were identified in the remaining 7 (see Table 3). The other 7 children spontaneously withdrew from the study and were lost to follow-up.

**Table 3.** Mutations were identified, and therapy was initiated in 11 children, including 2 siblings, affected by Long QTc in the screening ECG and Holter ECG. Additionally, results of QTc in the ECG, Holter ECG, and the therapy undertaken by children with Long QTc in whom the effects of genetic investigations were negative.

SEX	MUTATION	Familiarity	QTc msc (ECG)	QTc msec (ECG Holter)	Therapy	Dosage	SEX	QTc msc (ECG)	QTc msec (ECG holter)	Therapy	Dosage
F	SCN5A (LQT3; c.647C>T)	No	427	438	Propranolol	2 mg/kg, 3 vv/die	F	468	460	Propranolol	2 mg/kg, 2 vv/die
F	KCNH2 (LQT2)	Father	458	461	Inderal	20 mg	F	402	441	Propranolol	2 mg/kg, 1 v/die
F	KCNH2 (LQT2; c.1196C>T)	No	438 + PR corto	-	-	-	F	413	449	Propranolol	2 mg/kg, 3 vv/die
F	KCNH2 (LQT2; c.3367G>C)	No	452	462	Propranolol	3 mg/kg, 3 vv/die	M	433	440	Propranolol	2 mg/kg, 3 vv/die
F	KCNH2 (LQT2; c.2560T>G), SCN5A (LQT3; c.5845G>A)	No	-	-	-	-	F	494	537	Nadolol	¾ cp (40 mg), 3 vv/die
F	KCNQ1 (polymorphism SCN5A-H558R, KCNH2-K897K, e KCNE1-S38G)	No	448	465	Propranolol	2 mg/kg, 3 vv/die	F	EXTEND ED	EXTEND ED	Metoprolol	8 mg, 2 vv/die
F	KCNQ1 (LQT1)	Mother	ND	ND	Nadolol	1,5 mg/Kg/die	F	EXTEND ED	EXTEND ED	Metoprolol	8 mg, 2 vv/die
F	KCNQ1 (LQT1)	Mom and maternal grandfather	ND	ND	-	-					
M	KCNQ1 (LQT1)	Mom and sister	434	465	Inderal	¾ + ½ + ½					
M*	KCNQ1 (LQT1)	Father (asymptomatic, QTc in the norm)	ND	ND	Nadolol	1 mg/Kg, 1 v/die					
M*	KCNQ1 (LQT1)	Father (asymptomatic QTc in the norm)	ND	ND	Nadolol	1 mg/Kg, 1 v/die					

\* brothers. Legend: N.O., not available.

Table 3 presents the genetic mutations detected in 11 children. One girl had an SCN5A mutation (c.647C>T). In three girls, a mutation in the KCNH2 gene (LQT2) was found; one girl had a nucleotide substitution in the KCNH2 gene (c.1196C>T), and another girl had a nucleotide substitution in the KCNH2 gene (c.3367G>C). In one girl, a nucleotide substitution was detected in both KCNH2 (c.2560T>G) and SCN5A (c.5845G>A). Follow-up data were not available for this girl. Patients were assessed in follow-up as asymptomatic, except for one with a KCNQ1 mutation and polymorphisms in other genes (SCN5A-H558R, KCNH2-K897K, KCNE1-S38G). This patient had a syncopal episode. Five children (three males and two siblings) had heterozygous mutations in KCNQ1 (LQT1). In the other male child, the LQT1 mutation was known in the family history (mother and sister of the child). Six children (3 females and 3 males, including two siblings) reported positive family history. Eight out of 11 children had a therapeutic protocol. Data for a female carrier of KCNH2 (c.2560T>G), SCN5A (c.5845G>A), and a female carrier of KCNQ1 (LQT1) were incomplete. A female carrier of KCNH2 (c.1196C>T) was not undergoing any therapy. In summary, the KCNQ1 (LQT1) mutation was present in 54.5% of patients, the KCNH2 (LQT2) mutation in 36.4% of patients, and the SCN5A (LQT3) mutation in 1 patient.

Table 3 also provides information on the results of neonatal ECG screening for Long QT in 7 children where specific mutations were not identified (6 females and 1 male). QTc values were



measured both through ECG and Holter ECG. QTc values varied among children (QTc: minimum 402 mcs - maximum 494 mcs; QTc Holter: minimum 440 mcs – maximum 537 mcs), indicating heterogeneity in QTc length. The prescribed therapy varies among patients and mainly uses beta-blockers such as propranolol, nadolol, and metoprolol. Propranolol is administered at 2 mg/kg dosages, with frequencies of 1 to 3 times daily, depending on the specific case. Nadolol is administered thrice daily at a dosage of ¾ tablet (40 mg). Metoprolol is administered at a dosage of 8 mg twice a day. In summary, the drugs used for the treatment of long QTc were Propranolol 39.8 % of children, Nadolol 22.2 % of children, Inderal 11.1 % of children, Metoprolol 11.1 % of children, and none 16.7 % of children.

Table 4 provides information on single ECG abnormalities found in children identified through neonatal screening for Long QT (total 4.3% of children). The most frequent were: patients with focal right bundle branch block were 54.5% of the total children with a single anomaly, patients with left axis deviation were 9.2% of the total single anomalies, patients with nonspecific ventricular repolarization abnormalities were 7.1% of the total single anomalies, patients with ventricular extrasystole were 4.6% of the total subjects with single anomalies, patients with supraventricular extrasystole were 4.5% of the total single anomalies, and patients with complete right bundle branch block were 3.7% of the total single anomalies. These results suggest a variety of electrical heart anomalies in children at risk of Long QT, with a significant prevalence of focal right bundle branch block.

**Table 4.** Frequency of ECG abnormalities in the population of 42,200 study subjects identified by newborn screening by ECG.

SINGLE ECG ABNORMALITY	Patients, No. (Partial %)	MULTIPLE ECG ABNORMALITY	Patients, No. (Partial %)
Right bundle branch focal block	983 (54.5)	Right Bundle Branch Focal Block + Right Ventricular Prevalence	61
Left axial deviation	166 (9.2)	Right Bundle Branch Focal Block + Left Axial Deviation	26
Nonspecific abnormalities of ventricular repolarization	128 (7.1)	Right bundle branch focal block + Non-specific alterations of repolarization	8
Ventricular extrasystole	83 (4.6)	Right Bundle Branch Focal Block + Supraventricular Extrasystole	6
Supraventricular extrasystole	82 (4.5)	Right Bundle Branch Focal Block + Ventricular Extrasystole	6
Complete right bundle branch block	66 (3.7)	Right bundle branch focal block + High voltages of QRS	5
High Voltage QRS	46	Right Bundle Branch Focal Block + PQ at Upper Limits	5
Ventricular pre-excitation	32	Right bundle branch focal block + negative T wave	2
Increased P wave amplitude	28	Right Bundle Branch Focal Block + Inf Q Waves	2
FP at Upper Limits	27	Right Bundle Branch Focal Block + Right Ventricular Head + Left Axial Deviation	2
Low QRS voltages	20	Right bundle branch focal block + Sinus tachycardia	2
Tachycardia sinusale	20	Blocco focale di branca dx + Deviazione assiale sx + Extrasistolia sopraventricolare	1
Bradycardia sinusale relativa	18	Right Bundle Branch Focal Block + Supraventricular Extrasystole + Ventricular Extrasystole	1

FP at Lower Limits	16	Right bundle branch focal block + Ventricular parasystole	1
AV conduction at the sup limits	10	Right Bundle Branch Focal Block + Right Ventricular Prevalence + PQ at Lower Limits	1
Positive T	10	Right Branch Focal Block + Migrant Steplight	1
Ectopic atrial rhythm	9	Right bundle branch focal block + Right ventricular and atrial prevalence	1
Positive T-wave	8 (97.1)	Right Bundle Branch Focal Block + Right Ventricular Prevalence + PQ at Upper Limits	1
Migrant step marker	8	TOTAL Right bundle branch focal block	132 (66.7%)
Right Axial Deviation	7	Right ventricular head + left axial deviation	17
Left front hemiblock	5	Right Ventricular Head + Deep Q Waves	7
Delayed right intraventricular conduction	4	Right ventricular prevalence + PR at the experimental limits	6
Respiratory sinus arrhythmia	3	Right Ventricular Head + High QRS Voltages	4
ST Elevation	3	Right Ventricular Prevalence + Non- Specific Abnormalities of Ventricular Repolarization	4
Negative T	3	Right Ventricular Prevalence + Ventricular Extrasystole	4
Dextrocardia	2	Right Ventricular Head + Low QRS Voltages	4
QTc and PQ at the lower limits	2	Right Ventricular Prevalence + Nonspecific Abnormalities of Ventricular Repolarization	3
Ventricular hyperkinetic arrhythmia	1	Right Ventricular Prevalence + Supraventricular Extrasystole	3
Appearance S1-Q3	1	Right ventricular prevalence + PQ at upper limits	2
A-V Dissociation	1	Right Ventricular Head + Appearance S1-Q3	1
Right atrial engagement	1	Right Ventricular Prevalence + AV Conduction at Upper Limits	1
Increased amplitude P waves	1	TOTAL Right ventricular prevalence	56 (28.3%)
Septal Q waves	1	Supraventricular Extrasystole + Ventricular Extrasystole	7
Flat T Waves	1	Ventricular Pre-Excitation + Right Bundle Branch Focal Block	2
AV Conduction Extension	1	Ventricular Pre-Excitation + Right Ventricular Head	2
qR in inferolateral site	1 (2.5)	TOTAL Ventricular pre-excitation	4 (2%)
Biventricular overload s.	1	Left Axial Deviation + Sinus Tachycardia	1
Signs of bi-atrial engagement	1	Left front hemiblock + Left axial deviation	1

Right Overload	1	Biventricular Hypertrophy + Supraventricular Extrasystole	1
Right ventricular overload	1	PQ at Lower Limits + Supraventricular Extrasystole	1
Diphasic T	2	FP at Lower Limits + Probable Junctional Rhythm in Migrant Stepper	1
Paroxysmal supraventricular tachycardia	1	Ventricular Pre-Excitation + Supraventricular Extrasystole	1
Total	1805	Migrant Steplight + Supraventricular Extrasystole	1
		TOTAL	198

Table 4 also provides information on multiple ECG abnormalities found in children with focal right bundle branch block identified through neonatal ECG screening for Long QT (0.47% of children). The most frequent were focal right bundle branch block associated with right ventricular prevalence was 61% of the total children with multiple anomalies, focal right bundle branch block plus left axis deviation was 26% of the total children with various anomalies, patients with focal right bundle branch block associated with other electrical abnormalities were 66.7% of the total children with multiple ECG anomalies.

Table 5 provides information on the frequency of structural heart abnormalities associated with specific ECG characteristics in 267 patients (11.9% of the total patients with structural heart abnormalities). The most frequent were: patients with isolated PFO were 164 (61.4%), patients with PFO associated with ASD OS (Atrial septal defect ostium secundum) were 25 (9.4%), patients with PFO plus Mitral insufficiency were 21 (7.9%), and patients with PFO plus PDA were 12 (4.5%). These results indicate that PFO is the main structural heart abnormality observed in patients undergoing ECG screening and is often associated with other anatomical conditions such as atrial septal defect, mitral insufficiency, and patent ductus arteriosus.

**Table 5.** Frequency of congenital heart diseases and/or valvulopathies in the population with ECG abnormalities. Frequency of congenital heart diseases and/or valvulopathies in the studied population affected by prolonged QTc interval.

Structural alteration of the heart associated with ECG abnormalities	Patients, n. (%)	Multiple structural alterations of the heart associated with a prolongation of the QTc interval	Patients, n. (%)
PFO	164 (61.4)	PFO	72 (62.1)
PFO / DIA OS	25 (9.4)	PFO + DIV	6 (5.2)
PFO + Mitral insufficiency	21 (7.9)	PFO + PDA	4 (3.4)
PFO + PDA	12 (4.5)	PFO / DIA OS	3
PFO + DIV	6	PFO + Mitral insufficiency	3
PFO / DIA OS + Mitral insufficiency	3	PFO + Aortic insufficiency	1
PFO + PDA + Mitral insufficiency	3	PFO + Tricuspid insufficiency	1
PFO + Aortic insufficiency	2	DIA OS	12 (10.3)
PFO / DIA OS + DIV	1	DIA OS + IM	1
PFO / DIA OS + PDA	1	DIA OS + Itric	1
PFO + Aortic Coarctation + Mitral Insufficiency	1	DIA OS + Aortic dysplasia	1
PFO + Tricuspid insufficiency	1	PDA	4
PFO + Flow acceleration at the level of the aortic isthmus without obstructive gradient + Mitral insufficiency	2	DIV	3

Mitral insufficiency	12 (4.5)	Mitral insufficiency	2
DIA OS	2	Aortic Insufficiency	1
DIA OS + Tricuspid insufficiency	2	Pulmonary stenosis	1 (11)
PDA	2	TOTAL	125
PDA + Mitral insufficiency	2		
DIV	1		
Pulmonary insufficiency	1		
Tricuspid insufficiency	1		
Mild aortic insufficiency in apparently tricuspid valve	1		
Multiple ventricular echodense neoformations, referable in the first hypothesis to rhabdomyomas	1		
TOTAL	267		

Legend: DIA, atrial defect; DIV, interventricular defect; PFO, patent foramen ovale; PDA, patency of the duct of Botallo.

Table 5 also presents associations between positive screening for prolonged QTc interval, included in the follow-up, and structural heart abnormalities in 116 patients (5.17 %). In particular, the most frequent were: 62.1% had PFO associated with other structural abnormalities, 5.2% had PFO plus VSD, and 3.4% had PFO plus PDA. Finally, 10.3% of patients had ASD OS.

4. Discussion

This study analyzed the utility of neonatal ECG screening for diagnosing long QT syndrome, heart rhythm abnormalities, and structural heart conditions that could be responsible for neonatal and infant morbidity and mortality [41] [42]. In particular, a retrospective analysis was conducted over 16 years of ECG screening performed on 42,200 newborns, highlighting changes over time, gender differences, and the importance of specific diagnostic investigations in certain subgroups of children undergoing neonatal ECG screening for long QTc syndrome. Gender differences emerged significantly, especially in the male subgroup. The results of the Holter ECG indicate high sensitivity in detecting anomalies. The study also highlights average variations in the QTc interval over time, while average values during follow-up can be useful in assessing cardiovascular risk in children with prolonged QTc beyond a specific predefined value. Delayed diagnosis of critical congenital heart disease poses a severe risk of mortality, morbidity, and disability. The utility of ECG screening as a universal method to identify affected newborns was emphasized by Schwartz et al. in 2002 [39].

The physiopathological mechanisms leading to sudden infant death syndrome (SIDS) in infants are not fully understood. It has been suggested that arrhythmias and cardiovascular changes may be responsible for death in infants affected by SIDS [43], including prolongation of the QTc interval in the early years of life [26]. However, there are significant challenges in establishing a cardiac cause for SIDS [44]. Some hypotheses overlap; for example, the conceptual failure in respiration could include apnea, prone sleep position, and asphyxia, which might be considered connected to co-sleeping [45]. However, a crucial step in understanding the complex pathophysiology of SIDS was the establishment of the Triple-Risk Model, which successfully conceptualized epidemiological, physiological, and neuropathological data associated with SIDS [46].

Prolonged QT syndrome can cause abnormal heartbeats and an increased risk of sudden cardiac arrest [36]. Its estimated prevalence is around 1 case per 2,000-2,500 individuals [47]. Although long QT syndrome is rare, it can be hazardous in infants and children as their cardiovascular system is still in the developmental stage. Moreover, an abnormal heart rhythm, such as ventricular tachycardia or ventricular arrhythmia, could lead to sudden cardiac arrest [48]. Finally, structural heart abnormalities are congenital conditions that can contribute to an increased risk of sudden cardiac arrest [42].

The QTc undergoes a physiological prolongation from the second month of life, returning to normal values at six months. Some deaths labelled as SIDS may be due to a mechanism similar or identical to that responsible for long QT syndrome [27]. The prevalence of long QT syndrome varies from 1 in 20,000 to 1 in 5,000 [37]. A prospective study demonstrated that in 50% of SIDS victims, the QTc was  $> 435$  msec [40]. The QT interval was increased in SIDS victims (QTc  $\geq 440$  ms, exceeding the 97.5th percentile). The risk of SIDS in infants with QTc  $> 435$  ms was calculated to be 41 times higher than that of children with a normal QTc [26]. Long QT syndrome and SIDS share similar phenotypes, such as prolonged QTc interval, reduced parasympathetic tone, and/or autonomic nervous system imbalance [49].

The prevalence of long QT syndrome (LQTS) identified in children undergoing ECG screening for long QT is 5.32%. The prevalence of long QTc is 1 in 2381 (0.42 ‰), similar to that found in the study by Schwartz et al. (1 in 2,534) [37]. However, our data might be underestimated because follow-up data for all children are unavailable.

Long QT syndrome (LQTS) refers to a group of "channelopathies," disorders affecting cardiac ion channels, contributing to approximately 12% of SIDS cases [36]. Screening in the neonatal period allows the identification of "at-risk" infants before the peak incidence of SIDS (2-6 months).

We identified 11 children carrying pathogenic mutations of LQTS: 6 LQT1 (KCNQ1; 54.5%), 3 LQT2 (KCNH2; 27.3%), 1 LQT3 (SCN5A; 9.1%); 1 case (9.1%) presented a combined mutation of LQT1 (KCNH2) and LQT3 (SCN5A). About 10% of sudden infant deaths classified as SIDS are likely caused by LQTS [27]. Follow-up evaluation predominantly shows asymptomaticity, except for one case with KCNQ1 mutation that manifested a syncopal episode, emphasizing the importance of genotype-phenotype correlation. In the other children in our case series, the diagnosis of long QT syndrome was confirmed, but the genetic mutation was not identified.

Mutations in the LQT1 gene (KCNQ1) cause defects in potassium channels with an LQT1 phenotype, the most common form of Long QT Syndrome (LQTS). LQT1 carriers have a higher risk of ventricular arrhythmias and fatal events [50]. The distribution within the LQTS subgroups in our study confirms the prevalence of LQT1 compared to other variants, in line with literature data [37] [51]. Genetic screening has allowed the identification and genetic characterization of affected family members with the syndrome. The nucleotide substitution in the LQT3 gene (SCN5A; c.647C>T) has been described in patients with LQTS, Brugada syndrome, atrial fibrillation, and SIDS [52] [53]. Patients with LQT3 showed a rapid trajectory towards cardiac events, with 20% being fatal. In contrast, with one exception, both LQT1 and LQT2 patients had relatively benign clinical course and outcomes, with no deaths and only one heart transplant [54].

After the discovery of the first three Long QT Syndrome (LQTS) susceptibility genes (KCNQ1, KCNH2, and SCN5A), a total of 17 genes have been identified, with seven genes discovered by Ackerman et al. [30]. However, more than half of the genes reported as responsible for LQTS have limited or contested evidence supporting their causality in the disease [55].

Long QT Syndrome (LQTS) is typically inherited in an autosomal dominant manner. Most individuals diagnosed with LQTS have an affected parent, and the proportion of LQTS caused by a de novo pathogenic variant is small. The penetrance of the disorder can vary [56]. The study has demonstrated the potential of neonatal screening to identify families at risk of Long QT Syndrome. Therefore, the benefit of neonatal screening has been extended to the relatives of children with Long QT Syndrome. Neonatal ECG screening reveals variations in the length of the QTc interval, suggesting the need for comprehensive assessments even in the absence of specific genetic mutations.

The therapeutic management outlined in the children's protocol emphasizes the importance of early identification and personalized treatment. The prescribed therapy, based on beta-blockers such as propranolol, nadolol, and metoprolol, reflects a joint approach with dosages tailored to individual needs, underscoring the significance of personalized treatment in Long QT management.

Neonatal ECG screening facilitated the identification of cardiac rhythm anomalies, such as right bundle branch block (2.33%), left axis deviation (0.39%), and nonspecific ventricular repolarization anomalies (0.30%) of the total screened neonates. The most common combined ECG anomalies were right bundle branch block associated with right ventricular prevalence (0.14%) and right bundle



branch block associated with left axis deviation (0.06%). Therefore, echocardiographic assessment in our patients with prolonged QTc and/or other ECG abnormalities aided in identifying congenital heart defects (CHD), as reported in the literature [37].

Routine ECG screening is a valuable tool for identifying unrecognized congenital heart defects (CHD) not detected by prenatal ultrasound and neonatal examinations in asymptomatic patients [42]. A study reported that postnatal echocardiographic screening does not contribute to improving the detection rate of critical or severe heart defects in newborns without prenatal diagnosis or clinical signs. The study authors suggest conducting the examination a few months after birth, but it has a high rate of false positives [57].

In total, the structural heart abnormalities identified through neonatal ECG screening were 6.3‰, with Patent Foramen Ovale (PFO) alone (3.9‰) or associated with other cardiac anomalies (6.3‰) being the most frequent. Following this, mitral valve insufficiency was less frequently identified (0.28‰). Overall, the frequency of cardiac anomalies identified in children enrolled for serial neonatal ECG screening for suspected prolonged QTc was 5.57%, with PFO, either single (3.21%) or associated with other structural heart anomalies, being the most common (4.01%). Subsequently, isolated ostium secundum atrial septal defect (ASD) (5.3‰) or associated with other cardiac anomalies was less commonly observed (6.7‰). Echocardiographic evaluation in these patients with prolonged QTc and/or other ECG abnormalities facilitated the identification of congenital heart defects, as reported in the literature [37].

It has been reported that the overall incidence of Congenital Heart Defects (CHD) is approximately 6-9‰ [58]. However, neonatal clinical examination generally cannot detect all forms of CHD [59]. The incidence of congenital heart diseases in asymptomatic neonates born at high altitudes was 27.8%, with Ostium Secundum Atrial Septal Defect (ASD OS) (62.7%), Patent Ductus Arteriosus (PDA) (21.9%), Ventricular Septal Defect (VSD) (2.9%), and multiple defects (12.6%) being observed [60]. Almost all CHD cases were simple forms with left-to-right shunting, including ASD OS, PDA, and VSD [60].

Neonatal ECG screening aims to recognise cardiovascular morbidity and mortality risk-related cardiac anomalies. During the study, 5.3% of newborns undergoing neonatal ECG screening underwent cardiac follow-up with serial ECGs for prolonged QTc. At the end of the follow-up, 0.12% of the children had completed the follow-up. Of the enrolled children, 0.10% had undergone ECG Holter monitoring. Finally, 18 children had been diagnosed with prolonged QTc, of whom 11 had a identified genetic mutation responsible for long QT. The primary drug used to treat prolonged QT was propranolol.

Additionally, ECG screening identified cardiac rhythm abnormalities in 4.7% of the children. The most frequent isolated cardiac rhythm abnormality was right bundle branch block (54.5% of total isolated rhythm abnormalities), and right bundle branch block was associated with right ventricular prevalence (30.8% of total multiple cardiac rhythm abnormalities). Overall, right bundle branch block, associated with other cardiac rhythm anomalies, was found in 66.7% of total multiple cardiac rhythm abnormalities.

The echocardiographic examination identified structural heart anomalies in many children with ECG abnormalities. Specifically, the patent foramen ovale (PFO) was found in 61.4% of total cardiac anomalies. Furthermore, overall results from this study suggest that neonatal ECG screening is valuable in recognizing cardiac abnormalities associated with the risk of cardiovascular morbidity and mortality, and echocardiographic examination is an essential additional resource to confirm the presence of structural heart anomalies.

Expanded genetic investigations allowed the identification of mutations in family members, enabling them to access genetic counselling. Additionally, routine neonatal ECG screening facilitated the diagnosis of other arrhythmogenic or structural cardiovascular anomalies not identified in previous prenatal and neonatal examinations. Early diagnosis of these conditions in asymptomatic patients is encouraged to provide these infants with immediate access to medical or surgical therapy, thereby reducing mortality and morbidity.

Considering the lack of some follow-up data for children with prolonged QT, there appears to be a need to establish a data collection network to monitor children's evolution more thoroughly with prolonged QTc.

## 5. Conclusions

The study demonstrates straightforward clinical utility, emphasizing the importance of neonatal ECG screening between 20 and 40 days of life. This screening has proven effective in diagnosing long QT syndrome and other cardiac rhythm anomalies early, enabling suspicions about structural heart pathologies. Identifying genetic mutations, particularly channelopathies, in over half of the children with prolonged QT, highlights the possibility of early interventions such as treatment with beta-blockers. Cost-benefit assessment indicates that screening saves newborns with long QT syndrome and provides additional benefits by identifying mutations and/or QTc prolongations in family members. Moreover, detecting other ECG abnormalities and congenital heart diseases further expands the number of children benefiting from screening.

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**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki. Permission from the Ethics Committee was not required for this study as our Research Center is the national reference center for Sudden Unexplained Infant Death, in accordance with the Italian Law n. 31/2006.

**Informed Consent Statement:** This retrospective study utilized a dataset extracted from a database, which was anonymized and stripped of personally identifiable information. The study is grounded in pre-existing data, encompassing paper medical records securely stored in hospital cabinets with keys and electronic data recorded in password-protected computers accessible exclusively by authorized healthcare personnel. Attempting to contact and secure individual consent from each parent in a study of this magnitude proved impractical. In conclusion, the study delivers significant scientific benefits, with minimal risk to privacy.

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