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Rationale and Objectives for ECG Screening in Infancy

J. Philip Saul, MD, FHRS¹, Peter J. Schwartz, MD, FHRS², Michael J. Ackerman, MD, PhD³, and John K. Triedman, MD, FHRS⁴

¹ Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University, Columbus, OH, USA

² Center for Cardiac Arrhythmias of Genetic Origin, IRCCS Istituto Auxologico Italiano, Milano, Italy

³ Departments of Medicine, Pediatrics, and Molecular Pharmacology & Experimental Therapeutics; Divisions of Cardiovascular Medicine and Pediatric Cardiology; Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, MN, USA

⁴ Department of Cardiology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Abstract

Electrocardiographic (ECG) screening of infants and children who may be at risk for sudden cardiac death is controversial, and both rational and emotional arguments have often been given similar weights. The authors each have direct experience in this field, but have different backgrounds and have expressed divergent views on this topic. We attempted to build consensus among ourselves based on the available facts, in hopes of providing an unbiased review of the relevant science and policy issues in favor of or against ECG screening in infants and children. This report presents our shared view on this medically and societally important topic.

The long QT syndrome (LQTS) satisfies several criteria that may make ECG screening worthwhile: it is not rare (~1 in 2,000 births); ECG diagnosis is feasible and can be used to trigger appropriate genetic testing; it causes approximately 10% of cases of sudden infant death syndrome as well as deaths in childhood and later in life, and effective treatments are available. By stimulating cascade screening of family members, diagnosis of affected infants may also prompt identification of asymptomatic but affected individuals. Neonatal screening is cost-effective using conventional criteria, and with a QTc cutoff of 460 ms in two different ECGs the number of false positives is estimated to be low (~1 in 1,000).

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Address for correspondence: Peter J. Schwartz, MD Professor and Head Center for Cardiac Arrhythmias of Genetic Origin IRCCS Istituto Auxologico Italiano Casa di Cura San Carlo Via Pier Lombardo, 22 20135 Milan, Italy Tel. +390255000408 Fax +390255000411 peter.schwartz@unipv.it.

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It is our conclusion that parents of newborn children should be informed about LQTS, a life-threatening but very treatable disease of significant prevalence that may be diagnosed by a simple ECG.

Keywords

ECG screening; infants; long QT syndrome; sudden cardiac death

INTRODUCTION

Infants and children are vulnerable to undiagnosed and potentially lethal cardiovascular diseases. The younger age range also includes the clinically important group of infants at risk for Sudden Infant Death Syndrome (SIDS). In contrast to diagnosis and therapy, which usually are not highly contentious issues, screening for asymptomatic diseases may be highly controversial. This is especially true for electrocardiographic (ECG) screening for the prevention of sudden cardiac death in the young. Arguments for and against ECG screening policy often reflect personal and societal ideologies, and many experts in the field have held strong and predictable positions on this topic over long periods of time. Additionally, patient advocates and advocacy groups have assumed a prominent role in this debate, one that is by its nature emotionally charged. These factors interact with analysis of objective issues related to screening, and have complicated the possibility of reaching an evidence-based consensus.

The intent of this manuscript is to address objectively some of the uncertain issues surrounding ECG screening in younger children and infants. The four of us, because of our different training and experience, have held and expressed in the past somewhat different opinions on ECG screening. We now felt that an attempt to build a consensus among ourselves might allow us to create a relatively unbiased review of the relevant science and policy issues in favor of, or against, ECG screening in infants and/or children.

Here, we review the data underlying the rationale to consider ECG screening and present our views on this medically and societally important issue. While we recognize that there is ongoing debate regarding possible unintended costs and potential minor adverse effects of population based ECG screening, we will argue that epidemiological, clinical and genetic data exist to support disease specific ECG screening for LQTS in early infancy.

ECG Screening Principles

Some basic concepts that are relevant to ECG screening can be stated at the outset. The ECG alone should provide a reasonable probability of diagnosing the conditions being screened. These conditions should not be exceedingly rare in the population that is screened and these conditions should carry a significant risk of a life-threatening manifestation as a first event. In addition, relatively simple and effective therapies should be available for the prevention of lethal events. Of the known cardiovascular diseases predisposing to sudden death in asymptomatic young people, the long QT syndrome (LQTS) best meets all of these criteria. No studies have been performed to determine the clinical utility of screening in newborns,

who constitute an appropriate population for screening in many respects, and no randomized studies of the efficacy of ECG screening exist at all.

Screening for LQTS in Infants

LQTS is a genetic disorder characterized by QT prolongation, T wave abnormalities on the ECG, potentially life-threatening cardiac arrhythmias (leading to syncope, cardiac arrest or sudden death) often triggered by stress, and the availability of very effective therapies (1). The onset of life-threatening arrhythmias is gene-specific and occurs mostly below age 15 (Fig. 1) (2). Therapy with beta-blockers is indicated in all LQTS subgroups, and the effect of proper medical management is a marked reduction in mortality, which was nearly 50% in untreated syncopal patients in the 1980s (3), and with current management is approximately 1% over ~15 years follow-up for the overall LQTS population (1).

On the basis of the identification of disease-causing mutations in infants with a QTc >460 ms measured at 3–4 weeks of age in a cohort of more than 44,000 infants, the prevalence of LQTS has been estimated at about 1/2,000 live births in a population primarily of European descent (4). This prevalence estimate is similar to those observed in Japanese studies of infants (5) and school-aged children (6). This allows a relatively simple calculation of how many new neonatal cases of LQTS can be expected each year in any country with a similar genetic background. It has been established, again by the presence of disease-causing mutations, that approximately 10% of sudden infant deaths categorized as SIDS are likely caused by LQTS (7,8) and that LQTS contributes also to stillbirths (9,10).

The combined observations that cardiac arrest or sudden cardiac death (SCD) is the sentinel event in 13% of affected patients outside the neonatal period (11), and that mortality is dramatically reduced among patients appropriately treated (1), suggest that early therapy has the potential to prevent SCD in the affected children. Thus, expectant management of a patient with a known diagnosis of LQTS without therapy is no longer acceptable (1). Recognizing this, treatment with β -blockers is now considered to be a Class I or IIa guidelines recommendation for almost all patients with a clinical diagnosis of LQTS (12). It goes without saying that affected individuals not yet diagnosed escape the possibility of being treated. Hence, an important clinical objective should be to identify the largest possible number of affected individuals at the earliest possible time.

The estimated prevalence of LQTS at 1/2,000 live births (4) is higher than some prior studies (see below), and requires a brief comment. The data from the large prospective study referred to above are shown in Figure 2. While the point estimate of 1/2,500 births was derived from a precise calculation, a consideration of all the factors involved shows that this leads to a conservative estimate. Disease-causing mutations were found in 43% of the infants with a QTc >470 ms, and 29% of those with a QTc between 461 and 470 ms; however, genetic screening was only performed in 14 of 28 (50%) infants in this latter QTc range. When this is added to the high probability that among the 196 non-genotyped infants with a QTc between 450 and 460 ms there might be at least some LQTS mutation carriers, it is reasonable to assume that the prevalence of LQTS in neonates is closer to 1/2,000 (4). Finally, among patients with a definite clinical diagnosis of LQTS, approximately 20% are still genotype-negative. Thus, a LQTS prevalence of 1/2,000 in screened infants may still be

a conservative estimate. With respectively 4 and 5.2 million live births per year in the United States and Europe (27 countries), the 1/2000 prevalence estimate predicts about 2,000 and 2,600 new cases of LQTS annually. Nationwide studies in Denmark and the Netherlands suggest that 50-60% of sudden unexpected deaths in children 1-18 years of age were due to inherited cardiac diseases (13).

Available data (4) suggest when to perform neonatal screening and how to design a reasonable protocol. In the 3rd-4th week of life, the QT pattern has stabilized in a timeframe prior to the most common window for SIDS vulnerability (i.e. 2-4 months of age). As errors in measurement are possible and developmental changes may still occur (14), it is recommended to act only on the basis of a second ECG which should be performed whenever the first one shows a QTc >460 ms. If the second ECG has a QTc >460 ms (1.3/1,000, Figure 2), LQTS genetic testing involving at least the 3 major LQTS-susceptibility genes is performed. If QTc is >470 ms (0.7/1000, Figure 2), or if a mutation is identified, β -blocker therapy is recommended. In the more common situation that the first QTc is between 450 and 460 ms (0.4/1000) it may be decided to obtain one or more follow-up ECGs over a short period of time to make an evaluation contingent on the outcome of multiple ECGs (Figure 3). In all cases, family history is considered as well as ECG assessment in first-degree relatives. In the prior study, >40% of the infants with a QTc >470 ms had a disease-causing mutation, and >90% of the infants whose QTc remained prolonged at 1 year of life had a positive genetic test (4).

Even though screening in the neonatal period allows to identify “at risk” infants prior to the peak incidence of SIDS (2-6 months), also screening in the elementary schools has a valid rationale, especially when feasibility is concerned, as shown by the large program ongoing in Japan. The most recent report from the Kanazawa City Prefecture assessed the prevalence of genetically identifiable LQTS in a population of 7961 1st and 7th graders who underwent ECG screening and determined that at least 1 in 2653 subjects had an identifiable LQTS mutation (6). This is remarkably similar to the prevalence of LQTS found by Schwartz et al in neonates (4), particularly considering that the data on SIDS (5) suggest that some LQTS neonates may not survive past 1 year of age.

Approximately 12-15% of newly identified patients with LQTS have *de novo* mutations, while the rest are inherited paternally or maternally, which may be undiagnosed in other family members. Once the infant with LQTS is diagnosed, the family members can be screened phenotypically, and when a disease-causing mutation has been found in the proband, mutation-specific “cascade screening” (15,16) is performed in the family. The overall process has the potential to identify both neonates and older related individuals who are affected, and to importantly reassure those family members that test negative for the mutation, a multiple bonus that increases the benefits that accrue from this approach.

Cost Effectiveness of Screening

Cost-effectiveness analysis is useful to assess the societal cost of specific medical interventions. This is especially true when the performance of comprehensive, population-based studies may be biased by predetermined public opinion or government policy. Using parameters such as cost per life-year saved, or quality adjusted life-year saved, the value of

the intervention can be assessed in relation to a standard threshold value that is societally accepted. For example, the cost of ECG screening in infants can be compared to the costs of vaccination for childhood infection, dialysis for chronic renal failure, or stenting for atherosclerotic coronary artery disease.

The available cost-effectiveness studies on screening approaches for the identification of asymptomatic youth at risk for SCD have had some common findings. First, because of its very low expense and relatively high sensitivity, the ECG is clearly a good candidate test to screen for the relevant diagnoses which may include other diseases besides LQTS. However, with the possible exception of Wolff-Parkinson-White syndrome, none of these diseases meet the criteria mentioned above for a successful screening effort as completely as LQTS. Second, the low prevalence of these diseases and imperfect specificity of the ECG necessarily result in some false positive screenings.

Two earlier studies have examined directly the utility of ECG screening for LQTS in infants and newborns (17,18). Zupancic et al. estimated the cost of universal screening performed for LQTS at day three of life to be about \$18,000 per life-year saved (17). This figure rose to over \$50,000 per life-year saved if the efficacy of β -blocker therapy at preventing sudden death was reduced from 100% to 35%, illustrating the importance of therapy efficacy. However, this study estimated the prevalence of LQTS at 1/10,000 (5 times lower than the current estimates), assumed that screening was performed in the maternity ward at day 3 of life, when the number of false positives is high (11), and targeted only decreases in mortality due to SIDS. Quaglini et al. provided a model with somewhat different goals and assumptions, based on ECG screening performed between 3 and 4 weeks of life and with the focus on prevention of sudden deaths due to LQTS not only in infancy (when they would be labeled as SIDS) but also later in life as well (18). They calculated a cost-effectiveness of under €12,000 per life-year (about US \$16,000). This study also noted that abnormalities in the neonatal ECG unexpectedly prompted the recognition of 4 cases of asymptomatic congenital heart diseases (coarctation of the aorta and anomalous origin of the left coronary artery) which escaped the initial medical visit.

Neither of these informative models included the cost of genotype testing, which was not commercially available at the time. Using the paradigm in Figure 3 and with the conservative estimate of 1.4/1,000 infants with a QTc >460 ms, one can expect approximately 6-7,000 infants per year undergoing genetic testing in the United States and in Europe. The advent of genetic testing will have differential effects on cost-effectiveness according to the country involved, as cost varies between €1,300 (US \$1,700) in Europe and US \$5,000 in the US. This will elevate the cost of the initial evaluation, but may possibly decrease total costs by appropriate reclassification of false positive patients, particularly as genetic identification of cases improves.

Significant questions have been raised regarding the effect of false positive findings as an unwanted cost of ECG screening for LQTS (19,20). It is important to understand that the threshold QTc used for diagnosis is the primary determinant of the test sensitivity and specificity. The available data (4) point to a low expected false positive rate for those with a

QTc >460 ms (<1/1,000, ~38/43,080 neonates in Figure 2), but to about 4.5/1000 for those with a QTc >450 ms.

Potential Limitations and Issues for ECG Screening in Infancy

It seems likely that practical barriers could make implementation of a neonatal ECG screening program somewhat more difficult in the US than in other Countries at the present time. These barriers include issues related to reimbursement, availability of equipment, an appropriate professional workforce, and refinement of the methodology for the identification of appropriate QTc thresholds. A few of the important factors yet to be resolved in this area are the reproducibility of detection of LQTS in the neonatal population and the likely response to treatment, both of which affect the utility of screening diagnosis.

Reproducibility has two components. First, the accuracy of automated QTc measurement algorithms, which are widely used in clinical practice and may be biased in comparison to the manual measurement techniques used in most research populations, must be validated. Second, although the prevalence of LQTS mutations has been estimated to be about 1/2,000 in Italian white neonates (4), no similarly large study of neonates has been performed in another population. However, this estimate is strongly supported by a recent, smaller study performed in Japan (5). In over 4,000 infants screened in the first month of life with an ECG, complemented when possible by genetic testing, the prevalence of LQTS was found to be approximately 1/1,500, but with a larger probability error due to the smaller population. Especially important is the observation that 0.19% of Japanese infants had a QTc exceeding 460 ms, a value close to the 0.13% infants reported for whites (4). This represents a first and important validation for the concept that the prevalence of LQTS is similar across ethnically different populations.

With respect to response to therapy, the LQTS genotypes in the setting of SIDS appear to differ from those in the older population of LQTS patients, with a 50% vs 5-10% presence of sodium channel mutations (7,8,11). A possible explanation is that some infants, born with more malignant forms of LQTS, die before being counted in studies of older populations. Although the medical therapies known to be effective for LQTS are likely to have the same utility in the newborn population as in older populations, there is one important exception: those infants who suffer a cardiac arrest in the first year of life while being off therapy represent a subgroup at extremely high risk, poorly responsive to therapy and difficult to save without an ICD (21,22). Doubts have been raised about the efficacy of β -blockers for the LQT3 variant (23); however, data in a large population of >400 LQT3 patients indicate that β -blockers can be very effective, with a mortality below 3% among treated patients (24).

Consideration of the Optimal Time to Screen

Identification of children with diagnoses at risk for SCD at all ages would require, as a first step, ECG screening targeted specifically to detect LQTS in early infancy. To avoid the large variability of the QT interval present in the first week of life (14), which would increase the number of false positives, the screening should be performed, as recommended by the Guidelines of the European Society of Cardiology (25), in the 3rd-4th week of life thus allowing the identification of “at risk” infants prior to the risk period for SIDS (26). In

countries in which, for whatever organizational issues, screening in the first month of life would be too complex, a reasonable alternative is represented by the Japanese experience with ECG screening in the elementary schools (6).

A Debate on the Wisdom of Screening

Neonatal ECG screening is a controversial area, and a number of respected pediatricians and cardiologists are strongly opposed to it. What we have attempted to do here is to present, for an open discussion, our personal consensus on the evidence available to answer this question. These views should not be construed to represent an ideological position, but are based on the experience that each of us has accumulated in this specific field, as witnessed by our previous work.

We have agreed that among the congenital channelopathic/arrhythmic and cardiomyopathic syndromes with a propensity to cause SCD, LQTS best fulfills the various criteria that make ECG screening a desirable option. Although physiological changes in the ECG during neonatal transition preclude testing in the post-partum unit, it could be incorporated into the routine of well-child care in early infancy or, later on, in elementary schools. As to cost-effectiveness, multiple studies have suggested that ECG screening for LQTS in infants is comparable to other societally elected health interventions, and likely to be more cost-effective than ECG screening performed at older ages. Additionally, the identification of each affected infant may provide a multiplier effect, by permitting cascade screening and efficient identification of asymptomatic but nevertheless affected and potentially vulnerable family members. This value of this approach has already been shown in a general population, and should be considered to have an important role in any diagnostic scheme for LQTS, even though sometimes cascade screening starts only after a first patient in the family has already died (27). The serendipitous identification of a small number of infants with congenital heart disease for which early pre-symptomatic surgical correction can change prognosis is an additional non-negligible benefit of neonatal ECG screening (18). To prove the value of ECG screening, studies of the effectiveness of medical therapy for LQTS in patients diagnosed with this disease in early infancy will be useful.

Thus, we feel that there is at present sufficient evidence to propose ECG screening in infancy for LQTS. It is likely that implementation of screening for these patients will present logistical difficulties in implementation. However, this important issue while possibly affecting cost-effectiveness does not nullify the independent clinical value of early diagnosis of LQTS. With further accumulation of data, ECG screening could even be explored as a mandated or voluntary component of routine well-baby care. Regardless of whether this is adopted as a health policy mandate, provision of ECG screening should not be denied based on unresolved questions of its cost effectiveness, when requested by informed parents. Indeed, this may be the most critical issue: the parents of newborn children should be informed about LQTS, a complex, potentially life-threatening and treatable condition that may be diagnosed in infancy by ECG.

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LIST OF ABBREVIATIONS

ECG	ElectroCardioGraphic/ElectroCardioGram
LQTS	Long QT Syndrome
SCD	Sudden Cardiac Death
SIDS	Sudden Infant Death Syndrome

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Figure 1.

Kaplan-Meier cumulative survival curves showing time interval between birth and first cardiac event (syncope, resuscitated cardiac arrest, sudden death). Of note, figure and study do not include asymptomatic patients. LQT1 vs LQT2, $p < 0.0001$. LQT1 vs LQT3, $p = 0.0001$. LQT3 vs LQT2, $p = \text{NS}$. (From ref. 2)

Figure 2.

Distribution of 43,080 Caucasian neonates among 5 subgroups (absolute numbers and percentage), according to QTc duration on the screening ECG. Neonates positive at the genetic analysis are also reported (*From ref. 3*).

Screening ECG at 3-4 Weeks of Life

Figure 3.

Diagram for the steps which should follow neonatal ECG screening based on the QTc observed with the second ECG performed after that the first one had showed a QTc >450 ms.