Contribution of Long-QT Syndrome Genes to Sudden Infant Death Syndrome
Is It Time to Consider Newborn Electrocardiographic Screening?

Charles I. Berul, MD; James C. Perry, MD

Sudden infant death syndrome (SIDS) is defined as unexplained and unexpected death within the first year of life, without any known preexisting inciting conditions or obvious cause of death on postmortem examination. It remains the most common cause of infant death (excluding neonatal period) in developed countries, occurring in \( \approx 0.03\% \) to 0.1\% of live-born infants in the United States.\(^1\)

The precise mechanisms for SIDS, or “crib death,” are not known, although multiple hypotheses have been proposed over the years, including abnormal brainstem respiratory control of arousal, dysautonomia, and malignant cardiac bradyarrhythmias or tachyarrhythmias.\(^2\)–\(^4\) Genetic, developmental, and environmental risk factors for SIDS have been identified, such as premature birth, multiple gestations, being the sibling of a SIDS victim, maternal illicit drug use, prone sleeping position or bed sharing, and history of apnea/bradycardia or “near-miss SIDS” episodes.\(^3\)–\(^5\) Investigators have suggested respiratory control regulatory abnormalities, neurological developmental defects, and cardiac rhythm disorders, including QT prolongation and ventricular arrhythmias, as underpinnings of SIDS. Supporting these various hypotheses are common autopsy findings such as petechial hemorrhages, pulmonary congestion, and developmental defects in the brainstem and neurotransmitters.\(^4\)–\(^5\) Myriad diagnostic studies have been used for potential risk stratification of infants thought to be at higher risk for SIDS and have included electroencephalogram, pulse oximetry, 12-lead ECG, home apnea monitoring, and infant polysomnography sleep studies. The National Institutes of Health and the American Academy of Pediatrics have actively promoted the supine sleeping position for healthy term infants, and pediatricians have educated parents to put infants to sleep in the supine position or bed sharing, and history of apnea/hypopnea or tachyarrhythmias.2–4 Genetic, developmental, and environmental risk factors for SIDS have been identified, such as premature birth, multiple gestations, being the sibling of a SIDS victim, maternal illicit drug use, prone sleeping position or bed sharing, and history of apnea/bradycardia or “near-miss SIDS” episodes.3–5 Investigators have suggested respiratory control regulatory abnormalities, neurological developmental defects, and cardiac rhythm disorders, including QT prolongation and ventricular arrhythmias, as underpinnings of SIDS. Supporting these various hypotheses are common autopsy findings such as petechial hemorrhages, pulmonary congestion, and developmental defects in the brainstem and neurotransmitters.4–5 Myriad diagnostic studies have been used for potential risk stratification of infants thought to be at higher risk for SIDS and have included electroencephalogram, pulse oximetry, 12-lead ECG, home apnea monitoring, and infant polysomnography sleep studies. The National Institutes of Health and the American Academy of Pediatrics have actively promoted the supine sleeping position for healthy term infants, and pediatricians have educated parents to put infants to sleep in the supine position. This simple recommendation has, at least in part, contributed to a significant reduction in the incidence of SIDS.5

Death from cardiac causes is uncommon in infancy and is most often the result of cardiac electrical diseases such as the congenital long-QT syndromes (LQTS), severe structural congenital heart disease, and metabolic cardiomyopathies. In infants without a known antemortem diagnosis or abnormalities identified at autopsy, “SIDS” becomes the default diagnosis and accounts for the majority of cases. Although SIDS is clearly multifactorial, the potential cardiac causes of some SIDS cases include rhythm disturbances and congenital LQTS. However, most SIDS victims have normal QT intervals, no antecedent history of arrhythmia symptoms, and no known family history of QT prolongation, LQTS, or sudden death.

Clinical and Genetic Linkage of SIDS and LQTS

The link between SIDS and LQTS was initially suggested in the 1970s through the use of ECG data from parents of SIDS victims or near-SIDS survivors and showed QT prolongation in >25% of first-degree relatives.\(^6\) In the same year, a related hypothesis that SIDS was related to abnormalities in cardiac sympathetic innervation also was proposed.\(^8\) Over the subsequent decades, active investigation into the potential pathophysiological mechanisms leading to SIDS clarified the heterogeneous nature of the diagnosis. Accusations of infanticide complicated the evaluation of causation in some cases, particularly in families with multiple SIDS victims, thereby masking the determination of either an inherited or homicidal origin.

Given these clinical theories and case reports, it has been suggested that more widespread routine neonatal screening may have prognostic utility for SIDS. A large cohort study in 1998 demonstrated a correlation between neonatal QT prolongation and subsequent SIDS.\(^8\) This ambitious study was met with remarkable editorial controversy\(^10,11\) because it suggested that routine neonatal ECG screening might allow early identification and treatment of infants at risk for SIDS. Although a program of universal neonatal ECG screening may allow early detection of infants with QT prolongation (and other cardiac conduction abnormalities) at risk of SIDS, the practice raises concerns about clinical accuracy, physician resources, cost-effectiveness, medicolegal responsibility and risk, and parental anxiety. Despite an increased relative risk of a prolonged QT interval found on neonatal ECG, the low SIDS incidence resulting from LQTS lowers the positive predictive value to <1%, diminishing the power of ECG screening for SIDS risk stratification.\(^12\)
Molecular Genetic Linkage of SIDS and LQTS

The genetic causes of LQTS were first reported in the 1990s, yet the initial molecular correlation of LQTS genes with SIDS was not made until Schwartz and colleagues reported a case of a previously healthy infant with resuscitated sudden death and found marked QT prolongation and a spontaneous SCN5A sodium channel gene mutation. Both parents had a normal QTc on ECG, and the affected child did not inherit the SCN5A mutation. These investigators also showed a KCNQ1 mutation in a child who died of presumed SIDS. Another case report described an infant with a de novo mutation in SCN5A, along with marked QTc prolongation and ventricular tachycardia. However, this was not truly a SIDS case because the infant had an antemortem LQTS phenotype, but it provides an example of infantile LQTS with presumed risk of SIDS. Ackerman and colleagues screened genomic DNA from 93 SIDS victims and identified SCN5A defects in 2 of the cases.

In the present issue of Circulation, Arnestad and colleagues expand on these initial case reports of LQTS genes in SIDS victims by performing a comprehensive molecular genetic screen of 7 LQTS-associated ion channel–encoding genes in 201 SIDS cases in Norway. They identified 8 mutations and 7 rare variants in 19 of 201 cases (9.5%) not seen in 182 adult and infant controls. There were no epidemiological associations between SIDS victims with or without an LQTS gene variant, although maternal smoking and prone sleeping position were frequently observed. Another case report described an infant with a de novo mutation in SCN5A, along with marked QTc prolongation and ventricular tachycardia. However, this was not truly a SIDS case because the infant had an antemortem LQTS phenotype, but it provides an example of infantile LQTS with presumed risk of SIDS.

The authors hypothesize that this paradox is consistent with the increased likelihood of LQTS after infancy, in which SCN5A mutation in LQTS after infancy, in which SCN5A accounts for only ~10% of genotype-positive patients. The authors hypothesize that this paradox is consistent with the increased likelihood of SCN5A mutations causing life-threatening events during sleep, when SIDS typically occurs. Because the DNA data were anonymous, familial ECG or genetic screening was not possible, and unfortunately, no family history data are available for these SIDS victims, precluding the determination of whether these were spontaneous mutations or inherited LQTS.

The authors conclude that this study provides support for the recommendation of widespread newborn ECG screening to identify LQTS before the onset of symptoms or sudden death. The cost-effectiveness of this approach would vary widely by region and by healthcare system and is critically dependent on multiple factors, including the cost of testing, accuracy of interpretation, the cost and psychosocial factors of managing false-positive ECGs, and efficacy of treatment for true positives with LQTS. Death in the first year of life suggests a highly malignant disease and, along with the relatively high prevalence of SCN5A mutations, brings into question the potential efficacy of prevention by using mainly β-adrenergic–blocking drugs for SIDS (or infantile presentation of LQTS). More interventional therapeutic approaches (such as epicardial pacemakers, implantable cardioverter-defibrillators, and left cardiac sympathetic denervation) might be necessary to protect these high-risk infants from sudden cardiac death. The use of implantable cardioverter-defibrillators in infants requires novel implantation techniques and infers an entirely different risk-to-benefit analysis.

Given the growing consistency of these molecular autopsy reports, the challenge is for medical caretakers of infants to provide a cost-effective and efficient means for presymptomatic detection of LQTS to reduce the morbidity and mortality of the subset of SIDS etiologically related to LQTS genes and to determine whether newborn ECG screening is appropriate. The sensitivity and specificity of QT measurements on the infant ECG obviously are dependent on the threshold cutoff values we designate as abnormal, and a single QTc measurement on a resting ECG does not identify all infants with congenital LQTS. In the prior prospective study, the eCG was obtained in the first week of life, at which time transitional QT prolongation is relatively common. The 2 cost-effectiveness analyses differ in the proposed ECG acquisition time, which may alter the conclusions with regard to diagnostic accuracy on the basis of the input assumptions. Defining the acceptable balance between missing those infants truly at risk of sudden death as a result of LQTS and overdiaagnosing LQTS in those with borderline QT prolongation will need to take into account the multitude of factors alluded to above. Finally, because SIDS is a complex, multifactorial diagnosis, of which LQTS is only a small subset, an ECG will not identify the vast majority of infants at risk for SIDS.

Conclusions

SIDS is a heterogeneous diagnosis of exclusion, resulting from multiple origins. The study by Arnestad and colleagues strengthens the molecular evidence that some SIDS cases result from cardiac electrical diseases such as congenital LQTS. This well-designed study furthers our comprehension of the genetic basis of arrhythmia disorders and heterogeneous potential mechanisms of arrhythmogenesis in SIDS. The study provides additional data for subsequent discussion of the benefit of newborn ECG screening programs.

Disclosures

None.

References

5. Fleming P, Blair P, McKenna J. More interventional therapeutic approaches (such as epicardial pacemakers, implantable cardioverter-defibrillators, and left cardiac sympathetic denervation) might be necessary to protect these high-risk infants from sudden cardiac death. The use of implantable cardioverter-defibrillators in infants requires novel implantation techniques and infers an entirely different risk-to-benefit analysis.

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References


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