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A Neonate with Susceptibility to Long QT Syndrome Type 6 who Presented with Ventricular Fibrillation and Sudden Unexpected Infant Death

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 19-day
Final Diagnosis: 19 day old neonate with susceptibility to Long QT syndrome • ventricular fibrillation
Symptoms: Cardiac arrest • cardiac arrhythmia • encephalopathy
Medication: —
Clinical Procedure: Cardioversion
Specialty: Pediatrics and Neonatology

Objective: Rare disease
Background: This is a case of a neonate with susceptibility to long QT syndrome (LQTS) who presented with a sudden unexpected infant death. Experts continue to debate whether universal electrocardiogram (ECG) screening of all newborns is feasible, practical, and cost-effective.
Case Report: A 19-day-old neonate was found unresponsive by her mother. ECG showed ventricular fibrillation and a combination of a lidocaine drip plus multiple defibrillations converted the rhythm to normal sinus. Unfortunately, MRI brain imaging showed multiple infarcts and EEG showed burst suppression pattern with frequent seizures; life supportive treatment was stopped and the infant died. Genetic testing revealed two mutations in the KCNE2 gene consistent with susceptibility to LQTS type 6.
Conclusions: We believe this case is the first to demonstrate both a precipitating electrocardiographic and genetic cause of death for an infant with LQTS, showing a cause-and-effect relationship between LQTS mutation, ventricular arrhythmia, and death. We wonder whether universal ECG newborn screening to prevent LQTS death could have saved this baby.

MeSH Keywords: Infant, Newborn • Long QT Syndrome • Mass Screening • Sudden Infant Death • Ventricular Fibrillation

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Background

This case describes a neonate who presented with sudden unexpected infant death due to long QT syndrome (LQTS) and raises the question: "Is it now time for universal electrocardiogram (ECG) screening for all newborns?"

Case Report

A female neonate who had otherwise been healthy was found by her mother to be unresponsive on day of life 19. The infant was rushed to the emergency department and found to be in pulseless cardiac arrest with ventricular fibrillation. Cardiac defibrillation converted the rhythm back to normal sinus rhythm (Figure 1). A lidocaine drip was started but the patient continued to go in and out of ventricular fibrillation a total of 21 times. With each defibrillation, she quickly converted back to normal sinus rhythm. Eventually her rhythm stabilized.

An echocardiogram was performed which revealed no gross abnormalities. An ECG showed a prolonged QT interval of 465 milliseconds (msec) (Figure 2). Even though an acute cardiac event can lead to a prolonged QT, genetic testing and work-up for LQTS was undertaken. There was no history of sudden death or syncope in the family. ECGs from the available family members were normal and blood from the baby was obtained for LQTS gene panel testing. The FAMILION Genetic Test for LQTS from the Transgenomic Lab (New Haven, Connecticut, USA) sequenced the complete open reading frame, splice junctions, and flanking regions of the genes KCNQ1, KCNH2, SCN5a, KCNE1, and KCNE2. The test returned positive for two different mutations in gene KCNE2 (Ile 20 Asn and Arg 27 His), a gene associated with LQTS type 6. These mutations were classified as Class II or possible deleterious mutations. According to the test result, approximately 5% of patients without LQTS will exhibit Class II mutations.

A magnetic resonance image (MRI) of the patient's brain showed restricted diffusion in the posterior parietal lobes and occipital lobes bilaterally and possibly restricted diffusion in the left cerebellar hemisphere, consistent with multiple infarcts (Figures 3, 4), and the baby was severely encephalopathic with a burst suppression pattern on EEG and extremely frequent electrographic seizures. Therefore, life supportive treatment was discontinued. We recommended that the baby's family obtain genetic testing for LQTS. The father declined genetic testing despite encouragement. The mother obtained genetic testing which was positive for one of the infant's deleterious mutations (KCNE2 Arg 27 His). We recommended testing for other maternal family members. Unfortunately, the mother's family has not undergone genetic testing at the time of this case report.

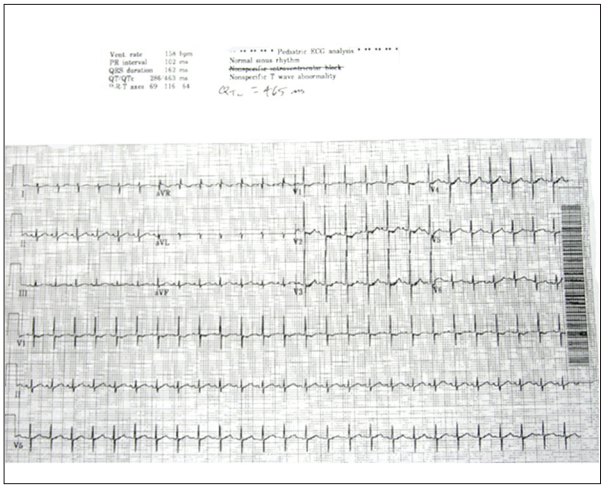

Figure 2. A 12-lead ECG after 21 cardiac defibrillations. QTc hand-measured by a pediatric cardiologist was 465 msec.

Discussion

To our knowledge, this is the first case demonstrating evidence of both a lethal arrhythmia as a precipitating event and a genetic diagnosis indicating susceptibility to LQTS for an infant who might have otherwise died of sudden infant death syndrome (SIDS) [1–5]. The infant tested positive for two LQTS mutations in gene KCNE2 and had a prolonged QT interval of 465 msec.

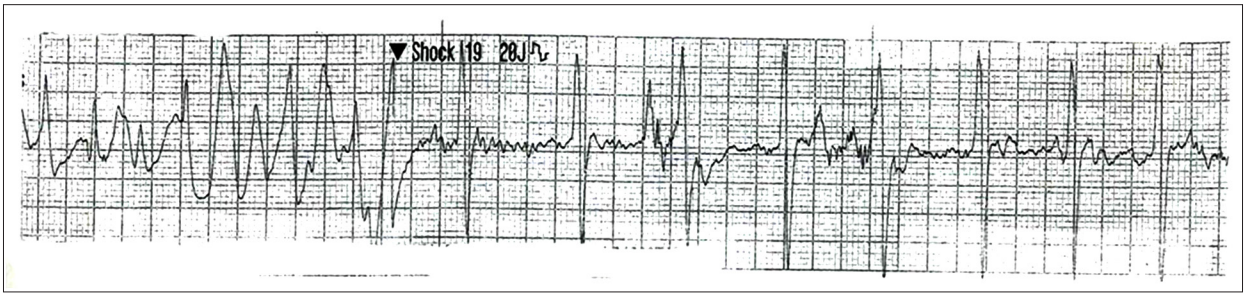

Figure 1. A rhythm tracing of the infant showing ventricular fibrillation converting to normal sinus rhythm after the 19th defibrillation. The triangle shows when the shock was administered.

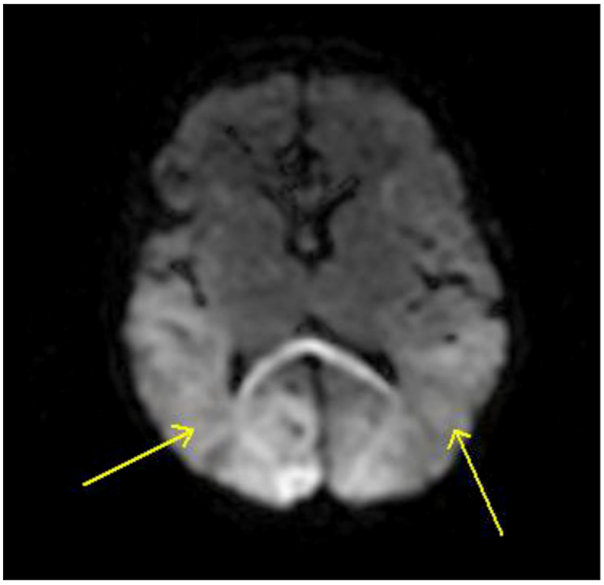

Figure 3. MRI brain diffusion-weighted sequences "demonstrate restricted diffusion in the posterior parietal lobes and occipital lobes bilaterally. There may be restricted diffusion in the left cerebellar hemisphere. Findings consistent with infarcts" per pediatric radiologist. Image reviewed by a pediatric neurologist who agreed with the findings.

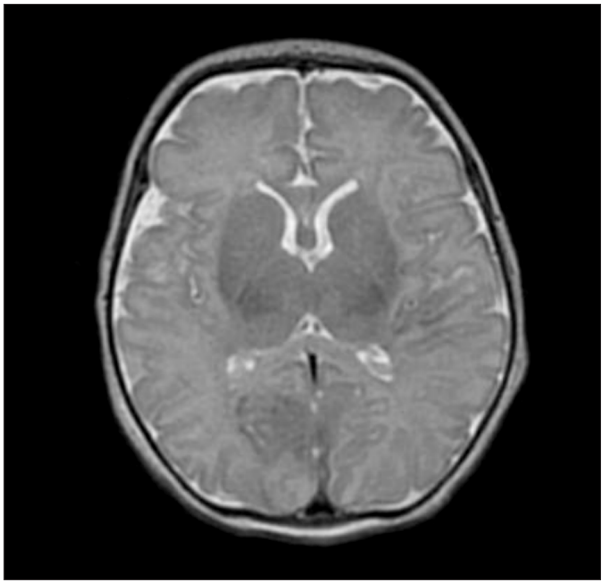

Figure 4. MRI brain T2-weighted imaging showing underlying normal brain structure.

LQTS is an electrophysiologic cardiac disorder characterized by QT interval prolongation. A mutation in one or more of 15 genes are known to be associated with LQTS; however, approximately 20% of families with a firm clinical diagnosis of LQTS do not have a defect in any of those 15 genes. [6] It is estimated that 60–75% of LQTS cases will have a mutation in the KCNQ1, KCNH2, or SCN5A genes (LQTS type 1, 2, and 3). Mutations in the other 12 genes only make up about 1% of LQTS cases. Long QT syndrome type 6 is associated with a mutation in the KCNE2 gene located at the 21q22.11 chromosome locus, and is associated with a potassium voltage gated channel [6]. In about 4–10% of individuals with LQTS, two pathogenic variations are found (digenic/biallelic inheritance). These individuals have a more severe phenotype [6]. LQTS, including type 6, is typically inherited in an autosomal dominant manner. Therefore, once a diagnosis is made, it is important to offer testing to first-degree relatives and extended relatives as indicated. The mother of this infant tested positive for one of the infant's mutations on the KCNE2 gene. Since the father declined genetic testing, we do not know whether the other mutation was inherited from him or *de novo*. It is possible that the infant may have had a different mutation on each of her alleles.

The most common symptom in an individual with LQTS is syncope, but only 50% or fewer of untreated individuals with a variant in one of the 15 genes will exhibit symptoms [6]. In some instances, LQTS will lead to ventricular fibrillation, cardiac arrest, and sudden death [6]. The life threatening arrhythmias are most likely to occur in persons under the age of 15 [7]. Beta-blocker medication is the primary treatment for LQTS, but in some cases an implantable cardioverter-defibrillator (ICD) and/or left cardiac sympathetic denervation is needed. ICD therapy should be considered for asymptomatic individuals with two or more pathogenic variants on molecular testing [6]. Another high-risk group includes infants who suffer a cardiac arrest during the first year of life. They are poorly responsive to beta-blocker therapy and may be difficult to save without an ICD [7]. Treatment has profoundly reduced mortality. In the 1980s, mortality was nearly 50% in untreated LQTS syncopal patients, but with current management the mortality is now less than 1% [7,8].

We wonder whether universal ECG newborn screening to prevent LQTS death could have saved the baby in this case report. While the baby's death cannot be assigned as a SIDS death because the infant was evaluated by an emergency room team who promptly recognized ventricular fibrillation, the infant would have likely died at home without explanation. Sudden infant death syndrome is assigned to infant deaths that cannot be explained after a thorough case investigation, including a scene investigation, autopsy, and review of the clinical history [9]. The incidence of SIDS has been decreasing since the back-to-sleep campaign, but has now stabilized at about 0.5–0.6 per 1,000 live births in the United States [10]. For the sake of discussion, we will review the association of prolonged QT interval and SIDS. After evaluating 34,442 Italian newborns from 1976 to 1994, Schwartz et al. reported a significant association with a prolonged mean corrected QT interval (QTc) and

SIDS [11]. The mean QTc, measured on the third or fourth day of life, of infants who eventually died of SIDS, was statistically longer than that of infants who survived to one year of age (435±45 msec *vs.* 400±20 msec, $p<0.01$). Because of these findings, Schwartz et al. suggested that routine neonatal screening by ECG and prophylaxis with beta-blockers may be warranted.

A flurry of responses from leading experts ensued. They argued that because prior studies had not shown ventricular arrhythmias prior to SIDS, we could not "assume that a cause-and-effect relationship between prolonged QT interval and SIDS exists" [12–14]. Furthermore, experts argued that several studies and at least one large study of 7,254 infants contradicted the Italian data [15–17]. Schwartz et al. countered, however, that "even though [the authors of the study of 7,254 infants] concluded that there was no significant difference between victims of SIDS and controls, 6 of the 15 infants who died of SIDS (40 percent) had a QTc exceeding the 90th percentile for the study population" [11]. Opponents of neonatal screening with ECG argued that the variability of QTc within the first week of life, errors in QTc measurement, an anticipated high false positive rate depending on the QTc cutoff, practical barriers of reimbursement, availability of equipment, and appropriate professional workforce, in addition to cost for screening and genetic testing, made screening "neither prudent nor practical" [17–24]. In a 2010 survey of North American pediatric cardiologists, only 10% would agree to a mandate for ECG screening [25].

Despite the controversy, Japan now has universal ECG screening of students in 1st, 7th, and 10th grades [26]. Furthermore, the Italian Ministry of Health funded a prospective "pilot" ECG study of 50,000 infants to assess the feasibility and outcome of nationwide neonatal ECG screening [27]. From 2001 to 2006, Schwartz et al. enrolled newborns in 18 Italian maternity hospitals for ECG screening between the 15th and 25th day of life [28]. Using a cutoff of >450 msec, 236 out of 44,596 infants were identified for repeat ECG testing within one to two weeks. Using a cutoff of >470 msec initially, then later >460 msec, 59 of 236 infants were identified for genetic testing. Among genotyped infants, disease-causing mutations were found in 43% (12/28) of infants with QTc >470 and 29% (4/14) of infants with a QTc between 461 and 470 msec. These results provided the first direct evidence of the prevalence of LQTS and supported neonatal ECG screening with guided molecular testing. The project also identified 15 undiagnosed parents as well as 42 other undiagnosed family members with LQTS. At least 31 infants were treated with 2 mg/kg/day propranolol with no reported side effects and no reported symptoms of LQTS, such as neonatal death.

Several groups have since supported ECG screening in infancy to prevent LQTS-related death [7,8,29–32]. The estimated prevalence of LQTS is 1:2,000 [28]. Using ECG screening to guide genetic testing, 80% of individuals with LQTS could be identified, and many other family members could subsequently be diagnosed once the proband is identified. ECG screening would also identify other infants at risk for death, including those with coarctation of the aorta and anomalous origin of the left coronary artery from the pulmonary artery, diagnoses which can escape the first medical visit [27]. Treatment is extremely effective with minimal side effects [33]. Looking specifically at LQTS patients, screening can increase their expected survival by 7.6 years, making screening more cost-effective than previously estimated [19,27]. Experts now report that "it is advisable to genotype newborns in LQTS families and newborns found to have a clear QT prolongation during an ECG screening" [34].

Conclusions

We believe that our case is the first to demonstrate both a precipitating electrocardiographic and genetic cause of death for an infant with susceptibility to LQTS, showing a cause-and-effect relationship between LQTS mutation, ventricular arrhythmia, and death. We wonder whether universal ECG newborn screening to prevent LQTS death could have saved this baby.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

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