CASE REPORT

Syncope and cardiac arrest during strenuous exercise associated with a novel mutation in LQTS1

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Key Clinical Message

Exercise-induced syncope should alert clinicians to the possibility of LQTS and must be distinguished from other malignant causes of syncope such as hypertrophic cardiomyopathy, catecholaminergic ventricular tachycardia, and arrhythmogenic right ventricular cardiomyopathy. Emerging genotype–phenotype links have connected mutations resulting in LQTS with risk of developing atrial fibrillation and cardiomyopathy.

Keywords

Cardiac arrest, exercise-induced syncope, long QT syndrome, malignant syncope.

Introduction

Hereditary long QT syndrome (LQTS) is a genetic disorder resulting in delayed ventricular repolarization manifesting as a prolonged QT interval on the electrocardiogram and an increased propensity for polymorphic ventricular tachycardia (torsade de pointes), syncope, and sudden arrhythmic death in young adults without structural abnormalities. Originally described as Romano–Ward and Jervell and Lange-Nielsen syndromes, breakthroughs in genetic and molecular analyses have allowed for more specific descriptions of a similar disease phenotype [1]. Point mutations on five genes primarily affecting the function of the cardiac potassium current: KCNQ1 (LQTS1), KCNH2 (LQTS2), SCN5A (LQTS3), minK (LQTS5), and MirP1 (LQTS6) have been implicated. Mutations in the KCNQ1 gene have been reported in 39–62% of patients with autosomal-dominant LQTS where sudden cardiac death is often triggered by physical activity [2]. The clinical triad of atrial fibrillation, cardiomyopathy, and sudden cardiac death in association with LQTS has not been previously described. We report a case of cardiac arrest with vigorous exercise, paroxysmal atrial fibrillation, and development of cardiomyopathy where subsequent genetic analysis identified a novel mutation in the KCNQ1 gene and LQTS1.

Case

A 30-year-old African American male developed ventricular fibrillation and sudden cardiac death with strenuous boot camp exercises while training with the United States Marine Corps at the age of 23 years. He was successfully resuscitated in the field and emergently transported to a nearby hospital for further medical care. Ischemic workup and evaluation for secondary causes of sudden cardiac arrest in addition to echocardiography were reassuring. Serial electrocardiography led to a diagnosis of LQTS and the patient received an implantable cardioverter defibrillator. Four years after this episode the patient established care with our facility with evaluation diagnosing paroxysmal atrial fibrillation. Despite adequate rate control and routine medical care, the patient subsequently developed left ventricular systolic dysfunction in the following 2 years. Workup for secondary causes at the time of these new diagnoses was unremarkable. The patient’s medica-
tions included aspirin 81 mg daily, carvedilol 12.5 mg twice daily, simvastatin 20 mg daily, and lisinopril 10 mg daily. He noted that his father developed a cardiomyopathy at the age of 35 years.

Cardiovascular examination throughout his care was unremarkable. Laboratory workup was notable for normal serum calcium, potassium, and magnesium levels. Figure 1 displays his resting electrocardiogram showing a QT interval of 480 msec and rate corrected QT (QTc) interval of 522 msec. Transthoracic echocardiography showed moderate reduction in left ventricular systolic function with an estimated left ventricular ejection fraction of 40% in a global distribution. The left ventricular (LV) dysfunction was a new finding compared to prior echocardiograms and workup for ischemic or secondary causes of new onset LV dysfunction were unremarkable. Based on his history of sudden cardiac death, family history, and implications for his siblings and children, a recommendation was made for genetic analysis. Genetic testing (which includes complete coding region and splice junctions of the following 12 genes currently known to be associated with LQTS: KCNQ1, KCNH2, SCN5A, ANK2, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP9, and SNTA1) revealed a point mutation resulting in a change of codon configuration from amino acids sequence GAG (glutamic acid) to GGG (glycine) at the E146G position in the KCNQ1 gene using gene sequencing analysis.

Over continued follow-up, the patient suffered from multiple episodes of exercise-induced ventricular tachycardia terminated by defibrillator therapies.

**Discussion**

To the best of our knowledge, this is the first report of the novel, likely pathogenic E146G mutation that manifests as phenotypic LQTS1 resulting in sudden cardiac death, atrial fibrillation, and cardiomyopathy. The E146G mutation on the KCNQ1 gene results in a amino acid substitution that is predicted to alter secondary protein structure. Napolitano et al. [3] studied the E146K mutation, which lies in the same residue, and linked its association with LQTS1. Further support of the functional importance of this region of the gene is suggested by missense mutations (such as T144A, Q147R, and A150G) in nearby residues that have been reported in the Human Gene Mutation Database in association with LQTS and atrial fibrillation [4]. The E146G mutation was not observed in approximately 6500 individuals of European or African American heritage as part of the National Heart Lung Blood Institute (NHLBI) Exome Sequencing Project indicating it is not likely to represent a benign polymorphism [5]. Analogous to reports in families with LQTS3 syndrome, we hypothesize this mutation may be associated with left ventricular dysfunction based on the patient’s course and family history [6].

Syncope is a common presenting complaint, and it can be difficult to decide when to expand the evaluation beyond a thorough history and physical examination. This case illustrates the importance of recognizing exercise-induced symptoms in a patient’s history. LQTS1 may present with a mildly prolonged QT interval at baseline,
however the QT interval fails to shorten with increased chronotropy associated with exertion. This leads to an increase in the QTc interval with chronotropy and greater propensity of ventricular arrhythmia. Other arrhythmic syndromes such as pre-excited atrial fibrillation (atrial fibrillation with an accessory pathway/Wolff-Parkinson-White syndrome) and catecholaminergic polymorphic ventricular tachycardia in addition to structural diseases such as hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, anomalous origin of coronary arteries, occult coronary artery disease, and myocarditis (or prior myocarditis with subsequent ventricular scarring) can present with exertional syncope or cardiac arrest with exertion. The patient presented herein had a significantly prolonged QTc interval, T-wave inversions, and lateral Q waves on his ECG (Fig. 1) at baseline. These findings persisted as the patient recovered from cardiac arrest. The abnormal ECG did not demonstrate pathognomonic findings, and additional testing was required to assess for other structural abnormalities. The remaining evaluation was unremarkable, leading to the clinical diagnosis of LQTS1.

Although the risk of sudden cardiac death with vigorous exercise is a rare yet often publicized event, cardiac events are triggered by exercise in most patients with LQTS1 [7]. Societies such as the American Heart Association have advised patients with LQTS against participation in “high intensity” athletic or training activities [8] which contradict exercise recommendations for patients with chronic heart failure [9]. The lifetime risk of sudden cardiac death with LQTS1 is estimated at 3–5%. Our patient experienced one episode of exercise-induced sudden cardiac death as detailed above and multiple ICD therapies at later dates triggered by vigorous activity. Balancing the above recommendations for our patient with LQTS1 and cardiomyopathy, we suggested modest, monitored exercise.

In our case, the patient carried a clinical diagnosis of a disease with an autosomal-dominant inheritance pattern. He had a daughter and several siblings placing importance on the identification of disease causing mutations for counseling of his family members. Genetic testing, however, is not yet considered standard assessment for patients presenting with exertional syncope [10]. With regard to exercise recommendations, genotype–phenotype correlations lack granularity to assist in prediction of individual risk associated with exercise for patients with LQTS. Genetic testing of the most common genes involved in the LQTS has value in certain clinical scenarios. As in the case reported, identification of a point mutation in the proband facilitates screening of family members, may influence treatment decisions, and identify those with “carrier” status which could carry clinical implications for presymptomatic patients at potential future risk. Moreover, as mutation detection is vital to the development and role of genetic screening, novel findings add to the catalog of known mutations to help guide ongoing work analyzing the genotype–phenotype link.

In conclusion, the case we present highlights the importance of recognizing exercise-associated symptoms in patients with LQTS and differentiating this condition from others with predisposition for ventricular arrhythmias. Through genetic testing we found a novel, pathogenic mutation on the KCNQ1 gene leading to LQTS1 with possible genetic predisposition for development of atrial fibrillation and left ventricular systolic dysfunction. This adds to the growing understanding of the genetic basis behind LQTS and emerging discoveries between genotypic–phenotypic links in this syndrome. Targeted genetic testing in patients with high pretest probability of this disorder may influence management of patients and their family members. For our patient, we provided genetic counseling to discuss the implications of this finding for himself and his family, including targeted testing of the E146G variant in the KCNQ1 gene for his siblings and daughter. Clinicians should be alarmed when evaluating patients with exertional syncope and expedite workup with electrocardiograms, echocardiogram, long-term cardiac telemetry monitoring, and referral to specialists if the diagnosis remains unclear.

**Conflict of Interest**

None declared.

**References**

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