Familial long QT syndrome and late development of dilated cardiomyopathy in a child with a KCNQ1 mutation: A case report

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Introduction

Congenital long QT syndrome (LQTS) is an inherited cardiac channelopathy characterized by prolongation of the QT interval on electrocardiogram (ECG), and is associated with an increased risk of life-threatening ventricular arrhythmias. Mutations in over a dozen distinct genes have been implicated in the pathogenesis of this group of disorders.[1] LQTS type 1 (LQT1), the most prevalent LQTS subtype, is characterized by a heterozygous loss-of-function mutation in the KCNQ1 gene, which codes for the α-subunit of the delayed rectifier inward potassium ion channel. The association of LQTS with dilated cardiomyopathy (DCM) is rare but has been reported in the presence of sodium channel gene mutations, as seen in LQTS type 3. In this case report, we describe a patient with familial LQT1 (KCNQ1 mutation) identified in infancy who was subsequently diagnosed with severe DCM later in childhood.

Case report

A 2-day-old male infant underwent cardiology evaluation owing to a family history of LQTS. Evaluation of the extended family had previously been remarkable for multiple family members, including his mother, having a prolonged QTc on ECG screening. The patient's ECG demonstrated a QTc of 495 msec and abnormal T-wave morphology (Figure 1A). He was admitted to the hospital for initiation of propranolol. Genetic testing of the patient and multiple first- and second-degree maternal relatives identified the presence of a deleterious genetic mutation, KCNQ1 Ser 349 Ter, consistent with LQT1. The patient's older brother, who had previously been thought to be unaffected, was also found to be positive for the mutation and started on medication. The patient was maintained on propranolol until 4 years of age, and nadolol thereafter. Throughout this time he was clinically well, without palpitations, syncope, or documented arrhythmias, although his QTc remained prolonged on serial ECG evaluations. He underwent formal exercise testing at 7 years of age, which was notable for a prolonged QTc throughout exercise and recovery. There were no arrhythmias and he had a normal oxygen consumption of 40.5 mL/kg/min. He was active in multiple recreational sports, including basketball, lacrosse, and baseball; an automated external defibrillator was available for emergency use. Repeat exercise testing was performed at 8 years of age, which again demonstrated a prolonged QTc without ventricular ectopy. Oxygen consumption was not measured, but his physical working capacity was described as low (work rate 67 watts).

At 9 years of age, the patient was admitted to the hospital complaining of several days of diffuse abdominal pain, vomiting, diarrhea, and fatigue. He was admitted to the general pediatric service with a presumed diagnosis of viral gastroenteritis and discharged home the following day after receiving intravenous hydration. He presented to the emergency room 1 week later with continued gastrointestinal symptoms, as well as worsening fatigue and dyspnea. The initial physical examination was notable for tachypnea and intermittent retractions. On auscultation, a 1/6 holosystolic murmur was heard at the apex, with no other abnormalities. Hepatomegaly with tenderness to palpation was present. The initial laboratory evaluation was notable for an elevated B-type natriuretic peptide of 8578 pg/mL. A chest radiograph showed increased interstitial markings without pulmonary edema or cardiomegaly. His ECG showed new T wave changes and voltage criteria for left ventricular (LV) hypertrophy, but no evidence of arrhythmia (Figure 1B). A transthoracic echocardiogram was performed and demonstrated severely diminished LV ejection with a markedly dilated left atrium, a mildly dilated left ventricle, and moderate to severe mitral regurgitation. The LV ejection fraction (EF), as estimated by Simpson's rule (biplane), was 15%. Right ventricular (RV) ejection was decreased as well, but not as markedly as that of the left ventricle. There was

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KEY TEACHING POINTS

- An association between long QT syndrome and dilated cardiomyopathy has been previously described in the presence of SCN5A mutations and may represent a sodium channel "overlap syndrome" between channelopathies and cardiomyopathies.
- It is possible that molecular interaction between potassium channel mutations and other mutations in the cardiac sarcomere and mitochondria may lead to a phenotypic overlap syndrome between long QT syndrome and cardiomyopathy.
- Additional screening for cardiomyopathy may be warranted in patients with a variety of genetic channelopathies.

echocardiographic evidence of elevated pulmonary artery pressures with an RV pressure estimate of 38 mm Hg above central venous pressure and a pulmonary artery end-diastolic pressure estimated at 15 mm Hg using the modified Bernoulli equation (Figure 2). An infectious evaluation failed to show any evidence of active viral infection (blood polymerase chain reaction assays for adenovirus, influenza, parainfluenza, metapneumovirus, rhinovirus, enterovirus, cytomegalovirus, HHV-6, parechovirus, parvovirus B19, Epstein-Barr virus, and stool polymerase chain reaction assays for common gastrointestinal pathogens were all negative) or systemic inflammation (C-reactive protein <0.5 mg/dL, erythrocyte sedimentation rate 0 mm/h) and the troponin I was 0.01 ng/mL. He was treated with 2 g/kg of intravenous immunoglobulin, without improvement.

A metabolic evaluation (lactate, pyruvate, acylcarnitine profile, blood and urine carnitine levels, plasma amino acids, urine organic acid, and creatine kinase) was negative. Commercial genetic testing consisting of DNA sequencing for 51 known cardiomyopathy genes was performed by the Laboratory for Molecular Medicine (Boston, MA) and was notable for a variant of unknown significance in the titin gene (p.Asn18096Lys). A Combined Mito Genome Plus Mito 140 Nuclear Gene Panel (GeneDx, Gaithersburg, MD) was also performed and showed heterozygosity for a variant of unknown significance in the ACO2 gene (p.Arg142Gln) and heterozygosity for a variant of unknown significance in the NDUFA10 gene (p.Arg337His). Cardiac magnetic resonance imaging (MRI) was obtained and demonstrated moderate to severe LV dilation (end-diastolic volume 165 mL/m^2), severely diminished LV ejection (EF 21%), and moderately diminished

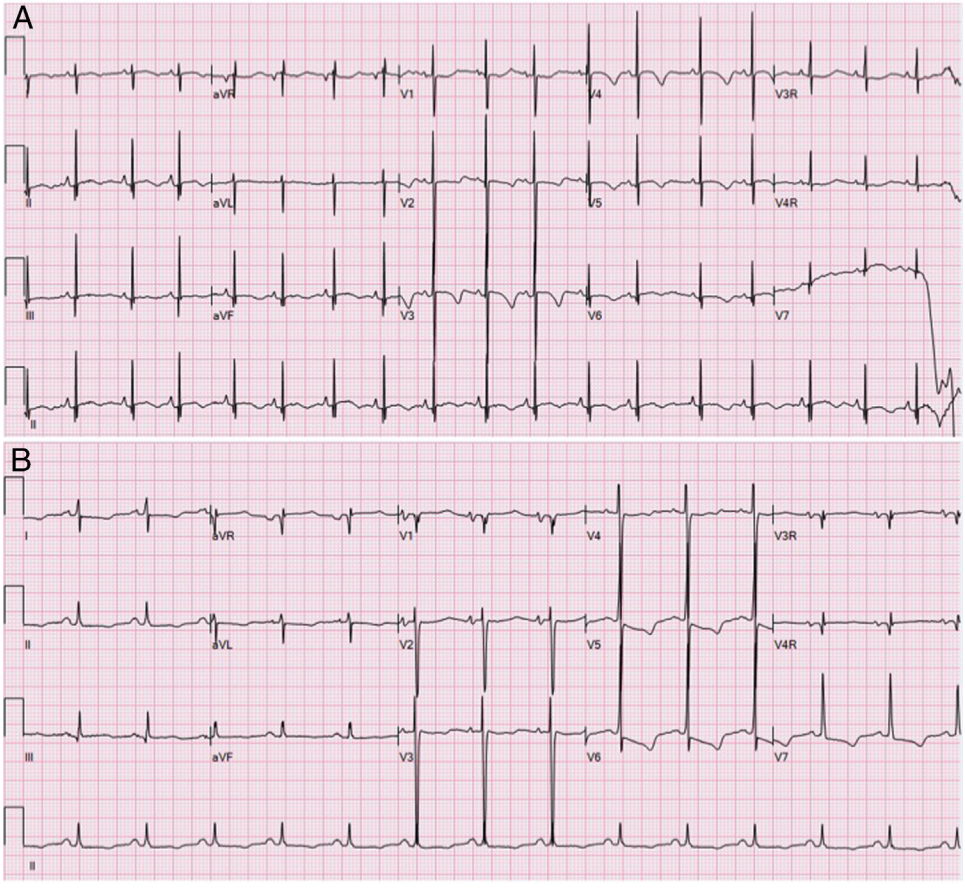

Figure 1 **A:** Twelve-lead electrocardiogram obtained at 2 days of life showing a corrected QT interval of 495 msec and nonspecific T wave abnormalities. **B:** Twelve-lead electrocardiogram obtained at time of presentation with heart failure at 9 years of age demonstrating new T wave changes and voltage criteria for left ventricular hypertrophy.