Congenital long QT syndrome: A difficult journey for one young survivor

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Introduction

Congenital long QT syndrome (LQTS) is characterized by prolongation of the repolarization phase after cardiac myocyte depolarization. It affects up to 1 in 2000 people and is a leading cause of sudden cardiac death (SCD) in the young.[1] To date, defects in 16 genes that code for transmembrane cardiac ion channels or accessory proteins have been implicated in more than 80% of cases. Patients with LQTS have a long QT interval on surface ECG and are predisposed to torsades de pointes (TdP). Infants with extremely prolonged repolarization may present with bradycardia from functional 2:1 AV block when the QT interval exceeds the P-P interval. We present a difficult case of LQTS in a highly affected child with a rescinded genetic diagnosis and multiple complications from medical therapies.

Case report

A biracial full-term female newborn presented on day of life 1 with 2:1 AV block and cardiac arrest due to an extremely long QT interval (>600 ms) and TdP. Her Caucasian mother had a normal ECG and a negative family history for SCD. Her African-American father was unavailable for clinical evaluation, and his family history was unknown. A single-chamber epicardial VVI pacemaker was placed through a limited sternotomy, and propranolol therapy up to 2 mg/kg/dose tid was initiated. By age 3 months, 2:1 AV block had resolved, but she developed culture-negative erosion of the pacemaker generator through the abdominal wall, which required removal of the chronic system and placement of a new single-chamber pacemaker system via left thoracotomy (Figure 1). Genetic testing in a research laboratory using Sanger sequencing for LQT1, LQT2, and LQT3 genes demonstrated a single sodium channel defect, SCN5A Leu 618 Phe, which supported the diagnosis of LQT3. Subsequent pacemaker interrogation demonstrated recurrent nonsustained TdP, so mexiletine was added to the medical regimen.

At 2 years of age, the patient had syncope due to nonsustained ventricular fibrillation (VF) despite pacing, high-dose propranolol at 2 mg/kg per dose tid, and mexiletine 4 mg/kg/dose. Her pacemaker system was upgraded to an epicardial implantable cardioverter-defibrillator (ICD) with addition of a subcutaneous coil and active abdominal generator. Nadolol 1 mg/kg/dose qd was added to the medical regimen for additional beta-blockade effect after a persistent high resting heart rate, normal blood pressures, and repeat TdP were demonstrated on propranolol and mexiletine (Figure 2A). The patient still received multiple subsequent appropriate shocks. Many ventricular arrhythmias occurred in the setting of low mexiletine levels due to parental medical noncompliance. Behavioral and family therapy were provided, and mexiletine drug levels were monitored. At the age of 3 years, the patient had repeat syncope because the epicardial ICD system failed to defibrillate several episodes of TdP and VF at maximum voltage output. The epicardial system was abandoned, and a dual-chamber endocardial ICD system was implanted through the left subclavian vein (Figure 2B). Because of the patient's small size (15 kg with a narrow chest diameter), the ICD can was electively placed in the abdomen. Despite atrial pacing at 80 bpm (to limit bradycardia and stabilize the heart rate) and weight and/or serum level adjusted doses of propranolol, nadolol, and mexiletine (see earlier), she continued to receive repeat appropriate shocks (Figure 3A). The patient was awake during several appropriate ICD shocks for TdP and subsequently developed posttraumatic stress disorder.

A left-sided cervical sympathectomy was performed when the patient was 4 years old. Commercial genetic testing at that time using Sanger sequencing for KCNQ1 (LQT1), KCNH2 (LQT2), SCN5A (LQT3), KCNe1 (LQT5), and KCNE2 (LQT6) confirmed an SCN5A Leu 618 Phe (exon 12, 1852 C>T, rs45488304) gene mutation classified as a class II variant (possible deleterious mutation). The ICD generator experienced battery depletion, which required

KEYWORDS Long QT syndrome; Implantable cardioverter-defibrillator; Epicardial

ABBREVIATIONS **ECG** = electrocardiogram; **ICD** = implantable cardioverter-defibrillator; **LQTS** = long QT syndrome; **SCD** = sudden cardiac death; **TdP** = torsades de pointes; **VF** = ventricular fibrillation

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KEY TEACHING POINTS

- Genetic testing for inherited arrhythmia syndromes and other disorders is probabilistic in nature, and interpretation of results may change over time as we amass detailed long-term clinical and genetic test data.
- The rate of complications for implanted cardiac devices in children is higher than in adults.

replacement when the patient was 9 years of age. When the patient was 11 years old, the right atrial endocardial pace-sense lead fractured, and the patient had repeat TdP and VF. A new endocardial right atrial lead was implanted and tunneled to the abdominal generator. The endocardial ventricular pace-sense lead failed after 9 years when the patient was 12 years old (noise was identified on ventricular electrograms before inappropriate therapies occurred). An open chest ICD extraction, right-sided cervical sympathectomy, tricuspid valve repair (endocardial right ventricular lead had perforated the anterior leaflet), and placement of a new epicardial ICD system were performed (Figure 3B).

The 12-year-old child went on to have more episodes of TdP and VF with successful shocks despite lenient

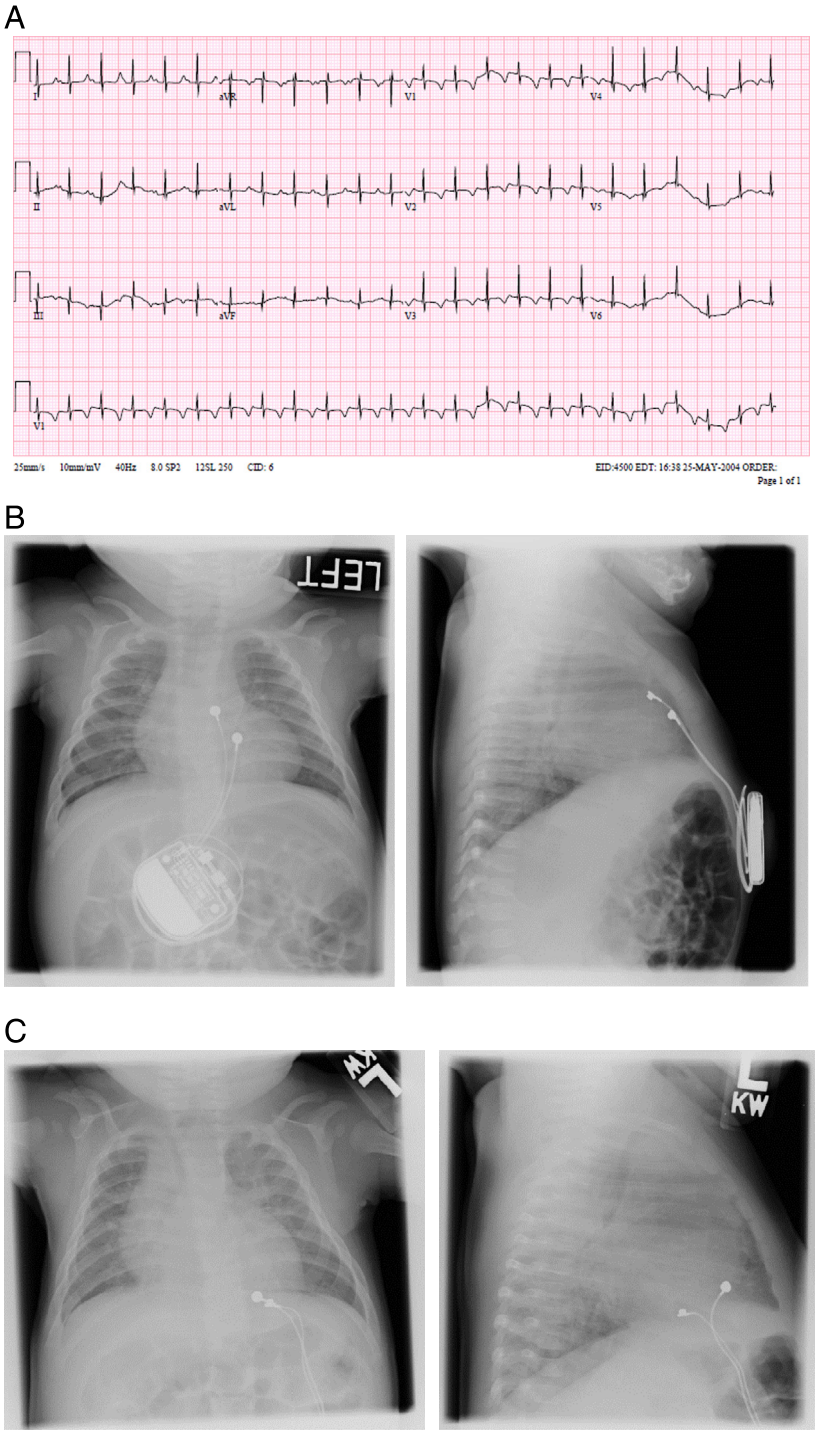

Figure 1 **A:** Resting ECG at age 3 months. **B:** Chest and abdomen X-ray films at the time of abdominal pacemaker generator erosion. **C:** Postoperative chest and abdomen X-ray films showing second single-chamber epicardial bipolar pacemaker system. At this time, the cardiac silhouette appeared enlarged but the echocardiogram was normal without effusion or chamber enlargement.

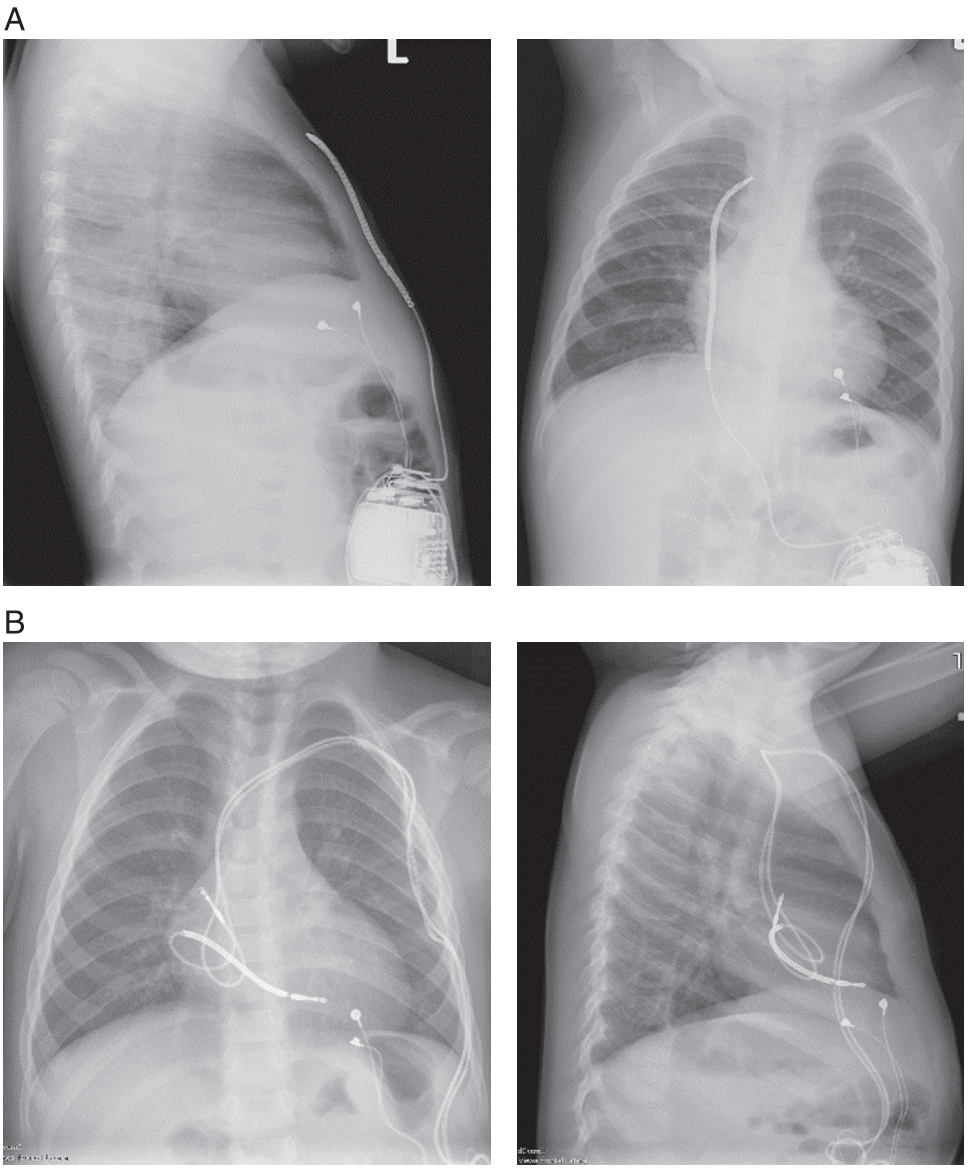

Figure 2 **A:** Chest and abdomen X-ray films at the time of epicardial bipolar pacemaker upgrade to an epicardial implantable cardioverter-defibrillator (ICD) system, including a subcutaneous coil placed to the left of the sternum and an abdominal ICD generator, at age 2 years. **B:** Chest and abdomen X-ray films at the time of endocardial ICD system placement, including extraction of subcutaneous ICD coil and addition of endocardial right atrial pacing and right ventricular single-coil ICD leads with tunneling of leads to the abdominal ICD generator, at age 3 years.

ventricular arrhythmia detection parameters, maximum propranolol, nadolol, and mexiletine doses, and therapeutic mexiletine levels. Recently, the patient's sodium channel SCNA5A Leu 618 Phe gene variation was downgraded from a possible LQTS-associated mutation to a likely benign class III variant that is common in patients of African-American descent, and we are now considering the withdrawal of mexiletine therapy. Therapy with alternative drugs, including spironolactone and ranolazine, will be considered in the future.

Discussion

Most patients with LQTS respond favorably to beta-blocker therapy, with resolution of TdP and syncope and mitigation of the risk for SCD. A minority of patients with more severe disease or medical noncompliance requires multiple drug therapy, ICD, or cervical sympathectomy. It is rare for patients with LQTS to have frequent TdP and VF in the setting of optimal medical and surgical management. This young child with an extremely long QT interval on surface ECG remains a genetic enigma and continues to suffer from TdP and VF despite our best efforts at prevention. She reminds us, with 41 appropriate high-voltage therapies before age 13 years, that despite the decades of knowledge we have accumulated about this prototypical inherited arrhythmia syndrome, we still have a long way to go before we fully understand all causes and optimal treatments for difficult cases of congenital LQTS.[2] With 7 pacemaker and ICD surgeries before age 13 years, this case also illustrates

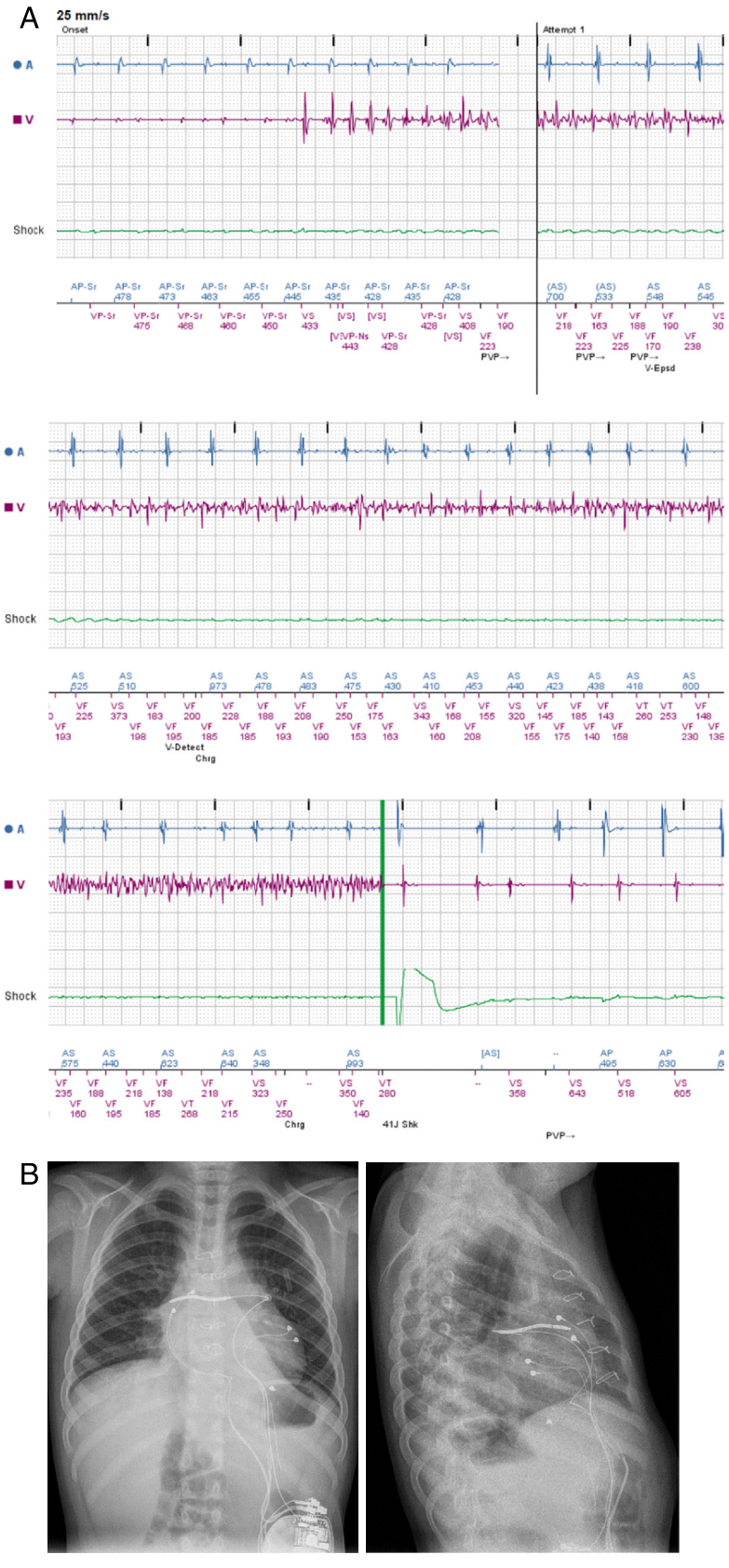

Figure 3 **A:** Stored ECGs during dual-chamber paced rhythm and episode of ventricular tachycardia that rapidly degenerated to ventricular fibrillation, triggering a successful implantable cardioverter-defibrillator (ICD) shock. **B:** Chest and abdomen X-ray films at the time of endocardial ICD system extraction and placement of a new epicardial system, including atrial and ventricular bipolar pace-sense leads, posterior and leftward pericardial coil, and abdominal ICD generator, at age 11 years.

the ongoing problems many children still face with repeat lead malfunctions, infections, and other complications despite modern era improvements in implanted cardiac device therapies.

References

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