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CASE REPORT
Arrhythmias/electrophysiology

Peripartum management of patient with long QT3 after successful implantable cardioverter defibrillator device discharge resulting in device failure: a case report

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Background Long QT3 syndrome type 3 (LQT3) is a gain of function mutation of the SCN5A gene that is inherited in an autosomal dominant fashion. Long QT3 syndrome type 3 results in an increase in arrhythmic events during rest, sleep, and bradycardia by extending the QT interval and inducing Torsades de pointes and sudden cardiac death. Attempting to block the sodium channel with Class I anti-arrhythmics or blocking adrenergic tone with beta-blockers especially in women has shown to be beneficial. There have been few large-scale studies on treating patients with LQT3 due to its lethality and underreported number of cases. Specifically, the safety and efficacy of pharmacologic treatment in pregnant LQT3 patients are unknown.

Case summary This case demonstrates the safe use of Mexiletine and Propranolol in a 3rd-trimester pregnant LQT3 patient after a presumed ventricular arrhythmia and device-lead electrical short from therapy rendered her implantable cardioverter defibrillator inoperable in a VVI mode (venticular demand pacing). With appropriate medications, the patient was safely monitored through the remainder of her pregnancy and safely delivered at 36 weeks of pregnancy a healthy baby girl. The daughter, heterozygous for LQT3, showed no evidence of intrauterine growth restriction or other side effects from the medications.

Discussion There are many variants of the SCN5A gene mutations that can lead to different phenotypes and not all mutations are responsive to the same medications. In this case, Mexiletine and Propranolol, both of which have only recently shown to benefit certain variants or LQT3 respectively, were safely started during the 3rd trimester of pregnancy without harming the foetus.

Keywords Long QT3 syndrome • Peripartum management • Mexiletine • ICD discharge • Life-Vest • case report

ESC Curriculum 9.8 Pregnancy with cardiac symptoms or disease • 5.10 Implantable cardioverter defibrillators

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Learning points

- Long QT3 syndrome has many genotypic and phenotypic variants that respond differently to medications, and therefore, require a full biophysical assessment of the individual channel mutants and genotypes before treatment.
- Mexiletine is a late sodium channel blocker that has recently been shown to shorten QT interval and reduce arrhythmic events in Long QT3 patients. Beta-blockers have only recently been shown to be beneficial in patients with Long QT3 given the concern for susceptibility to arrhythmia during periods of bradycardia.
- Propranolol and Mexiletine during the 3rd trimester of pregnancy were effective in treating a patient with long QT3 syndrome without harming the foetus.

Introduction

Long QT syndrome type 3 (LQT3) represents an autosomal dominant mutation of the gene SCN5A which codes for the Nav1.5 Na^+ channel α-subunit. There are over 103 mutations of the SCN5A gene leading to different phenotypes that can be influenced by both genetic and environmental factors including LQT3, Brugada syndrome, sick sinus syndrome, dilated cardiomyopathy, atrial fibrillation, and sudden infant death syndrome.[1,2] Long QT3 syndrome type 3 is caused by a gain of function of the late sodium channel leading to an excessive inflow of late sodium current in phase 2 of the cardiac action potential.[3] Clinically, the SCN5A mutation can cause arrhythmias during rest, sleep, or during periods of bradycardia, increasing the risk for torsades de pointes and sudden cardiac death.[1] The prevalence of long QT syndrome worldwide is ∼1 in 2000 to 1 in 5000, with LQT3 accounting for 10% of cases. LQTS is underreported due to the sudden cardiac death causing 180 000–450 000 deaths per year and the fact that 37% of genotyped LQTS patients have normal QT intervals.[4] Despite a reduced number of cardiac events compared with other LQTS, LQT3 leads to a disproportionate increase in lethality.[5] Treatment with sodium channel blockers such as Mexiletine (Class IB) has shown improvement in the condition.[6] Additionally, beta-blockers have shown benefit specifically in female patients with the condition.[7] The safety and efficacy of pharmacological treatment in LQT3 have not been extensively studied during pregnancy, because of small population sizes and the variation in genotype causing differences in response to treatment.[2] We present a rare case of a pregnant female who underwent medical management of her LQT3 after her implantable cardioverter defibrillator (ICD) fired.

Timeline

Date	Event
2002	Implantable cardioverter defibrillator (ICD) implanted after multiple syncopal events
	Started on Nadolol
2009	Official genetic testing confirming long QT3 (SCN5A variant)
2013	ICD right atrial lead upgrade
October 2018	Pregnant and stopped Nadolol
4 May 2019	Syncope with ICD firing and lead shortage during the Kentucky Derby
	Pacer in backup mode pacing 70 b.p.m.
	Started on Mexiletine 150 mg three times daily
	Discharged with Life-Vest
15 May 2019	Start Propranolol LA 60 mg daily
4 June 2019	Gave birth to baby girl
24 June 2019	Baby girl diagnosed with long QT3 SCN5A variant
14 August 2019	ICD device and leads extracted and replaced

Case presentation

The patient was a 29-year-old female G1P0 with a history of LQT3 diagnosed at age 13. Following recurrent syncopal episodes, she was diagnosed when genetic testing revealed an SCN5A Val 411 Met gain of function mutation (*Figure 1*). This genetic variant has been reported to be pathogenic in multiple unrelated people on Clinvar.[9] Functional studies indicate this variant results in the hyperpolarizing shifts in both conductance-voltage, inactivation-voltage, and a two-fold increase in the late sustained sodium current indicating an increased number of open-activated sodium channels.[10] At age 13, she was placed on Nadolol and had a Boston Scientific -Maple Grove, MN, USA) dual-chamber ICD with a Medtronic (Minneapolis, MN, USA) 6943 defibrillator lead and a Guidant 4469 right atrial pacing lead placed at due to multiple VT events in-hospital after syncopal events. The right atrial lead was eventually revised 11 years later with a Guidant 4472 right atrial pacing lead. Following implantation, she showed intermittent non-compliance with her Nadolol during adolescence causing 30 prior ICD shocks. She was placed on Midodrine at an outside hospital for episodes of recurrent orthostatic hypotension while on Nadolol. Both of her parents tested negative for the gene causing LQT3.

When she became pregnant with her first child at age 29, she discontinued Nadolol due to lack of recent events and her concern for intrauterine growth restriction (IUGR). Her electrocardiogram in *Figure 2* shows her prolonged QTc at 488 ms while not on treatment. While watching a controversial call during the

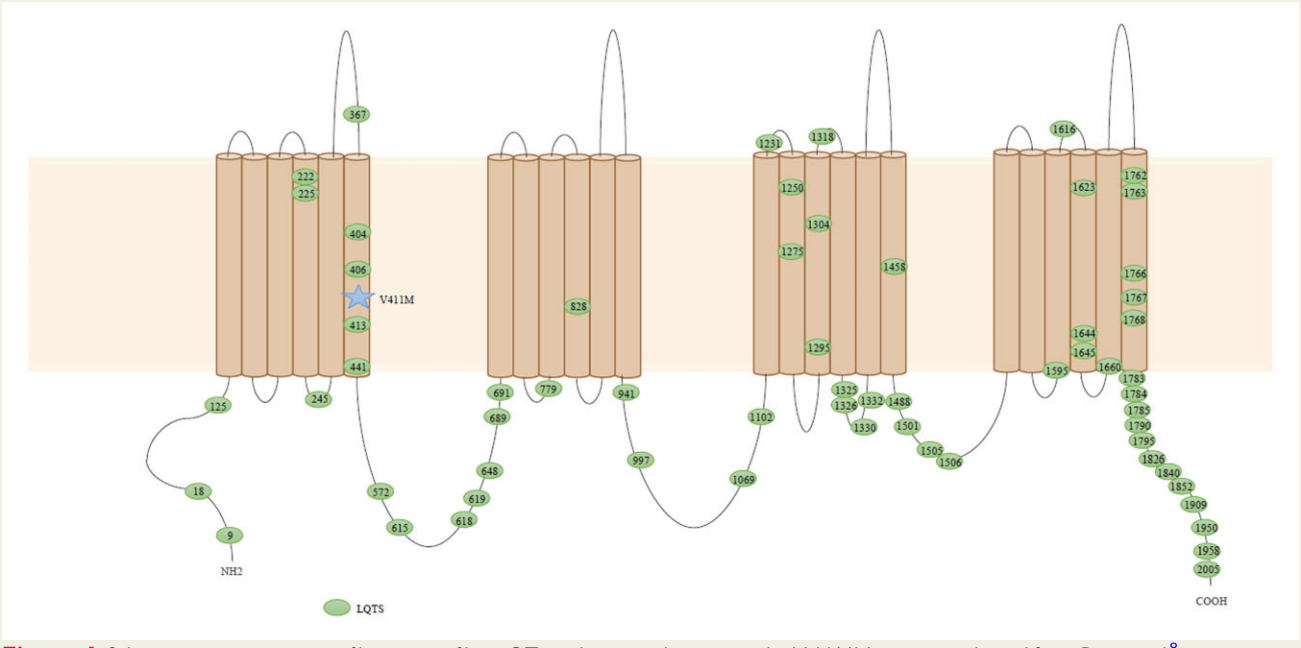

Figure 1 Schematic representation of locations of long QT syndrome with a star on the Val411Met variant adapted from Ruan *et al.*[8]

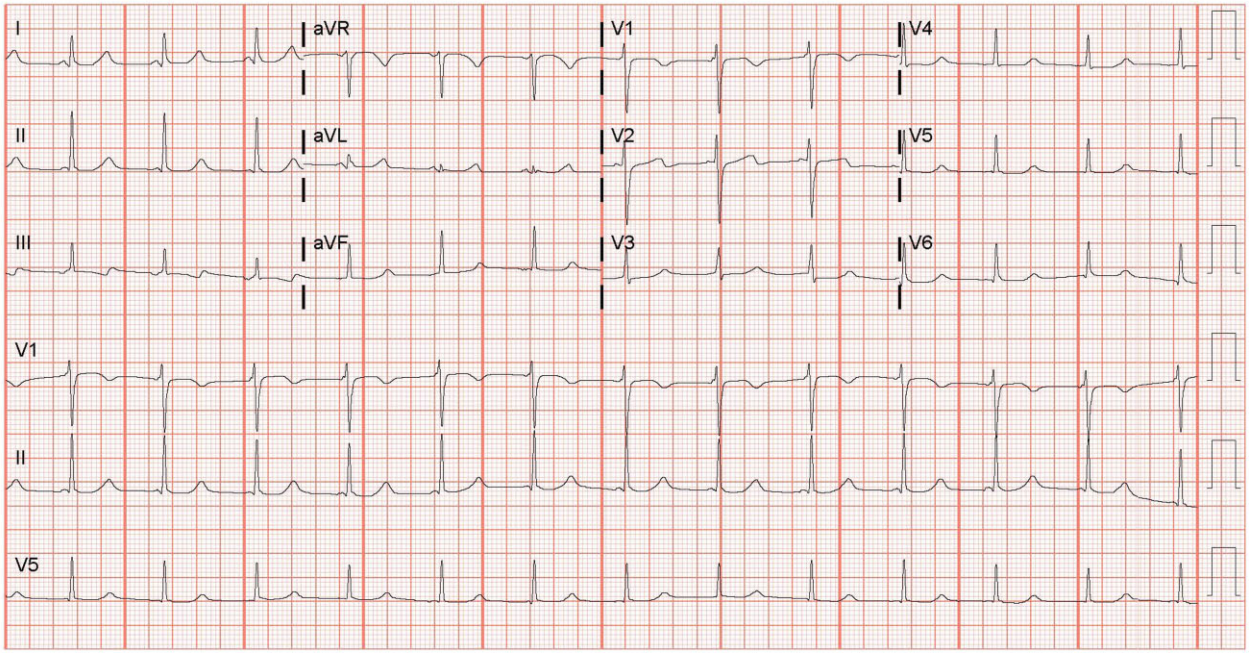

Figure 2 The patient's presenting electrocardiogram with QTc 488 ms.

Kentucky Derby at 31 weeks and 5 days pregnant, she had sudden loss of consciousness followed by firing of her ICD, which she felt as she was falling. Workup at an outside hospital revealed post-shock device failure with the ICD resorting to a VVI pacing mode (*Figure 3*). No retrievable information of the arrhythmia could be obtained from the device or programmer though Boston Scientific was contacted. Given the abrupt episode during a moment of high adrenergic stimulation, it is felt that her syncope was cardiac and arrhythmic in origin with an appropriate device discharge. Her most recent device interrogation in clinic 3 months prior

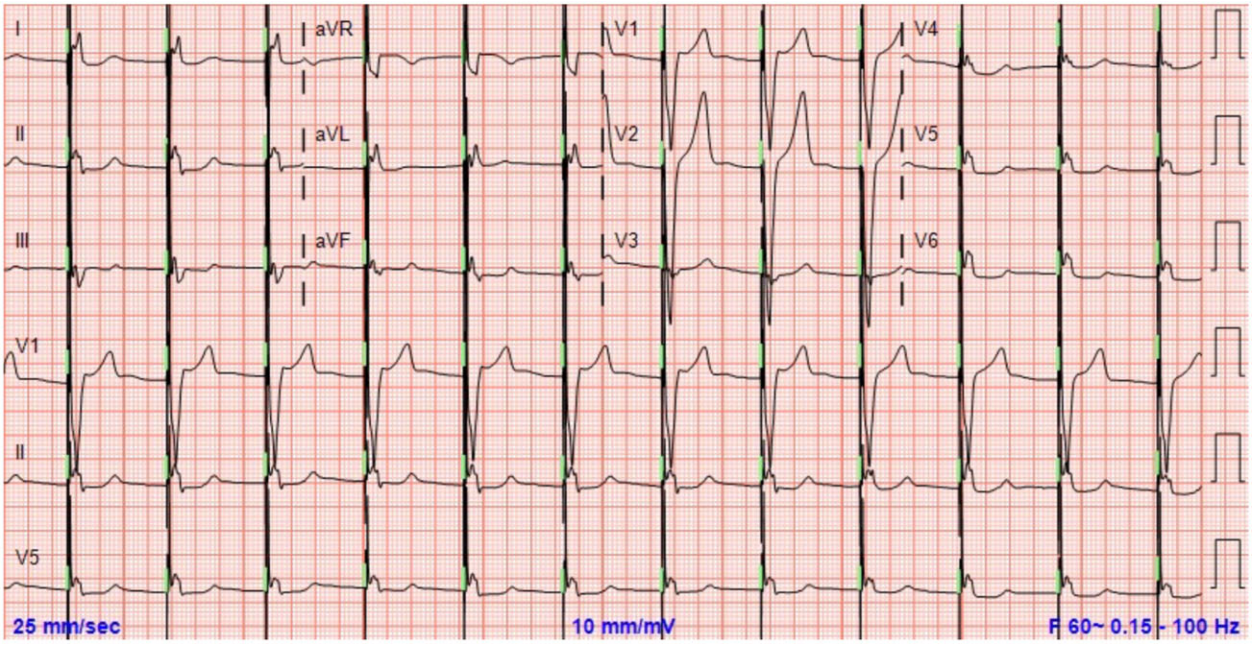

Figure 3 VVI pacing at heart rate of 70 and QTc 477.

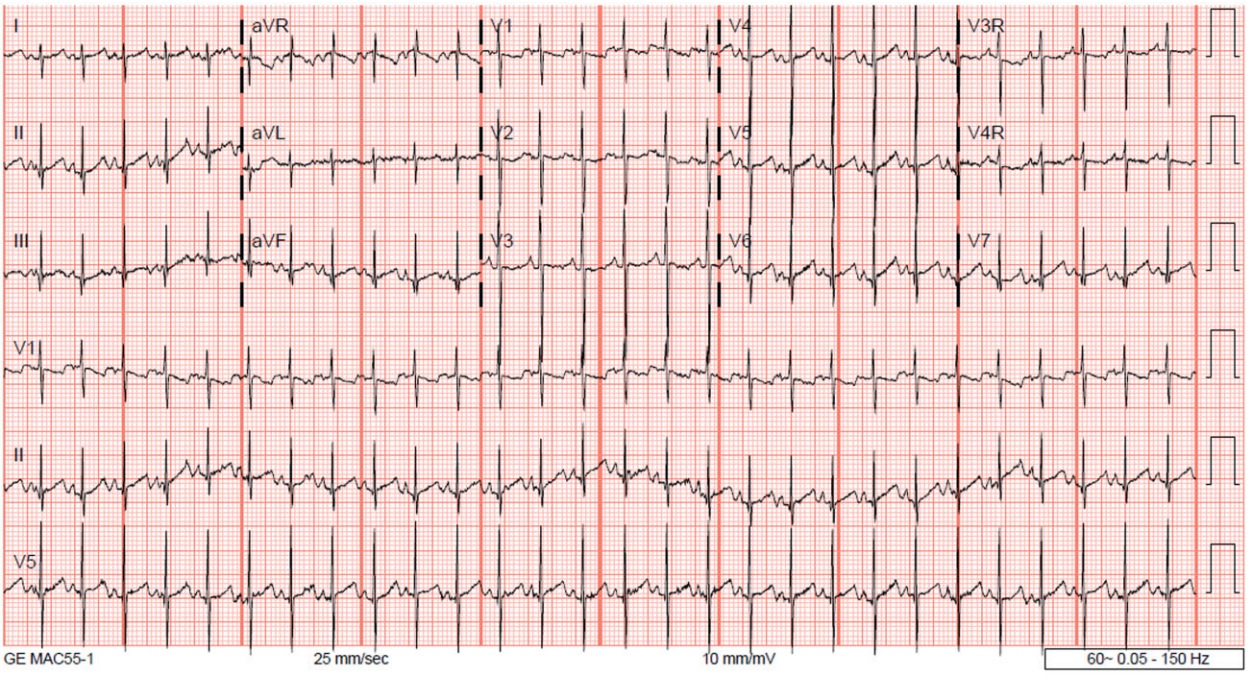

Figure 4 Electrocardiogram of baby of girl with heart rate 170 and QTc 487.

showed the device functioning well. After further discussion with the device manufacturer, it was felt that a short in the RV lead insulation that shorted back to the generator resulting in a catastrophic failure of the device. The device had then defaulted to its 'Safety Mode' VVI setting at a rate of 70 b.p.m., a setting infrequently encountered and usually only during catastrophic

Table 1 Comparison of LQT1-3 adapted from Sicouri and Antzelevitch[12]

Type of LQT	Chromosome	Ion channel	Prevalence	Treatment
1	11	$\downarrow I_{Ks}$	30–35%	Beta-blocker
2	7	$\downarrow I_{Kr}$	20–25%	Beta-blocker
3	3	$\uparrow$Late I_{Na}	5–10%	Beta-blocker, sodium channel blockers, pacemaker with defibrillator

events. No further interrogation of the device could be conducted after it entered 'Safety Mode'.

She was ultimately discharged with a Life-Vest (Zoll, Inc. Kelmsford, MA, USA), and started on Mexiletine 150 mg three times daily and Propranolol LA 60 mg daily. Trough levels of Mexiletine were monitored every 3–4 weeks and were adjusted as needed. Electrocardiograms were performed every 2 weeks to monitor QT segments that did not exceed 460 ms. There were no discharges of the Life-Vest. The patient was delivered by planned C-section to a baby girl at 36 weeks after preterm contractions. Her daughter did not meet the definition of IUGR or small for gestational age (weight <10th percentile).[11]

At 8 weeks post-partum, the ICD device and leads were successfully extracted. A new Boston Scientific Dynagen D152 ICD system with one right atrial (Medtronic 5076-15) and one right ventricular lead (Boston Scientific 0672) were placed without complication at an outside hospital. Her extracted device was not returned to Boston Scientific for further diagnostic evaluation. She has continued to do well with medications, including the ability to perform basic non-contact exercises. Genetic testing of the daughter identified the heterozygous presence of the familial SCN5A variant, c.1231>A, which is predicted to result in amino acid substitution Val411Met; she was subsequently started on Propranolol (*Figure 4*).

Discussion

Long QT syndromes from 1 to 17 have been identified with the most common cases being LQT1-3 (*Table 1*). Long QT3 syndrome type 3 is unique out of these due to properties of increased arrhythmic lethality and increased risk during episodes of bradycardia. There are many variants of the SCN5A gene mutations that can lead to different phenotypes. In order to treat patients with LQT3, patients should have a full biophysical assessment of the individual channel mutants and genotypes. Not all SCN5A mutations are responsive to the same medications as what benefits one patient may harm another patient.[13]

Mexiletine is a Class 1B antiarrhythmic late sodium channel blocker and pregnancy Class C medication.[14] It works by inhibiting inward sodium current, which then decreases the rate at which phase 0 rises and increases the effective refractory period to action potential duration ratio. Sodium channel blockers such as Mexiletine have some proven benefit in LQT3, especially in certain SCN5A genotypes compared with others.[2] Some variants of the SCN5A including I1771M, R1623Q, and A1186T have been shown to be resistant to Mexiletine.[15] Though there have been few studies of Mexiletine in pregnancy, there have not been any reported teratogenic long-term adverse effects in case studies.[16] Animal studies that received four times the maximum daily dose in humans did not show any teratogenic effects on the foetus though there was an increase in absorption of Mexiletine in the foetus.[17] Mexiletine was used in this patient due to history of VT and phenotype of her LQT3 diagnosis. This medication shortens the QT interval and also reduces arrhythmic events in LQT3 patients.[6] It also allows measurement of trough levels to ensure adequate dosing.

Beta-blockers, while well established in LQT1 and LQT2, have only recently been shown to have benefit in LQT3, especially in female patients.[7] These benefits persist despite a concern in LQT3 for susceptibility to arrhythmia during periods of bradycardia, and in many cases, atrial pacing can help overcome the ill effects of beta-blockers. The mechanism of benefit, however, remains undescribed: perhaps due to a suppression of early after depolarizations. In our patient, the device resorted to a VVI 70 mode, which likely provided protective benefit to the patient.

Not all beta-blockers are safe during pregnancy. Nadolol is a pregnancy category C medication with limited human studies. It has a long half-life and has low protein binding (30%) which increases the risk of exposing the foetus possible teratologic properties of Nadolol. Propranolol (pregnancy Class C) is preferred over Nadolol due to its shorter half-life and extensive protein binding (90%). There are more studies and patients on propranolol as it has been deemed safe during pregnancy. After multiple prospective clinical studies, the incidence of IUGR from propranolol is about 4%. Other documented foetal effects include bradycardia, birth apnoea, hypoglycaemia, IUGR, hyperbilirubinaemia, polycythaemia, prolonged labour, and single case of fetal death.[17] Atenolol should not be used as it has been shown to have ill-effects and is pregnancy Class D.[15]

Conclusion

In this case, both Propranolol and Mexiletine, as well as VVI pacing effectively prevented QT prolongation and further events, with no documented ill-effect on the foetus. This case illustrates the safe and effective use of the appropriate medical management of an LQT3 patient during the 3rd trimester of pregnancy utilizing a sodium channel blocker and a beta-blocker which allowed postponement of a high-risk device and lead extraction until after delivery.

Lead author biography

Dr Melissa Lee is currently a 4th year Internal Medicine Resident at Naval Medical Center Portsmouth in Virginia. She attended undergraduate and graduate school at University of California, San Diego from 2006 to 2012. She was a student at A.T. Still University—College of Osteopathic Medicine in Kirksville, Missouri from 2012 to 2016. She completed a Transitional Year at Beaumont Trenton in Michigan and then was an active duty General Medical Officer at Naval Health Clinic Cherry Point in New Bern, North Carolina for 2 years. She is going to complete Internal Medicine residency this year and then become Chief Resident. She is interested in a Cardiology Fellowship.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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