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Congenital long QT syndrome: Severe Torsades de pointes provoked by epinephrine in a digenic mutation carrier

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ABSTRACT

Congenital Long QT Syndrome (LQTS) is a potentially lethal cardiac channelopathy characterized by prolongation of the corrected QT (QTc) interval on the surface electrocardiogram. The hallmark phenotypic features are syncope, seizure or sudden death, however most of the mutation carriers are asymptomatic and their risk for arrhythmias such as Torsade de pointes (TdP) are low. We report a case of Long QT syndrome with a corrected QT of 520 ms. For symptom – arrhythmia correlation a loop recorder was implanted with no documented arrhythmias. Epinephrine testing was performed for clinical risk stratification leading to Torsades de pointes during recovery phase which required defibrillation. Genetic testing discovered two pathogenic heterozygous mutations in two different LQT genes (*SCN5A* and *KCNQ1*). We propose a calcium homeostasis mechanism for the interaction of both mutations that exaggerated the phenotype, while each mutation by itself is causing a relatively modest phenotype.

Introduction

Congenital Long QT syndrome (LQTS) is a genetic channelopathy with variable penetrance that is associated with increased propensity to syncope, polymorphic ventricular tachycardia (Torsades de Pointes; TdP), and sudden arrhythmic death.[1] Digenic mutations (two mutations in different genes) or more often compound heterozygosity (two different mutations in the same gene) in LQTS-related genes occurred in 2.0%–8.5% in published reports[2–5] and are associated with significantly longer QTc intervals[2,4,5] and more severe phenotypes.[2,4] In this report, we describe a case where severe TdP occurred and subsequently two pathogenic heterozygous mutations in two different LQT genes have been identified suggesting an interaction between both mutated gene products.

Case report

The proband is a 39 year-old female patient who was referred to us based on a resting QTc of 520 ms (Fig. 1) after a second episode of likely vasovagal syncope. The first episode occurred 6 years prior to the current presentation and was suggestive of vasovagal syncope. The second, more recent episode occurred during micturition and was preceded with nausea and dizziness. Apart from a corrected QT of 520 ms, no other abnormalities were seen on ECG. All other cardiac investigations including an echocardiogram and exercise stress test were unremarkable.

In view of a lack of symptom–rhythm correlation, she had a loop recorder implanted and was put on Nadolol which was gradually increased to 60 mg, twice daily. However, over a period of 12 months she did not have any syncope spells and no documented arrhythmias on the loop recorder. The family history revealed that her paternal uncle died of drowning at the age of 16 and her nephew (maternal brother's child) died suddenly at age of 4 months old.

For further risk stratification and to determine the type of LQTS we decided to perform an epinephrine drug challenge and started an incremental epinephrine infusion from 0.05 mcg per kg per minute up to 0.2 mcg per kg per minute after stopping Nadolol for a week. The QTc interval was calculated using the Bazett formula (QT divided by the square root of RR interval). The QTc prior to the epinephrine challenge was 567 ms and prolonged up to a maximum QTc of 596 ms at 0.2 mcg per kg per minute epinephrine

Abbreviations: LQTS, Long QT syndrome; QTc, Corrected QT interval; TdP, Torsade de pointes; VT, Ventricular tachycardia; ICD, Implantable cardioverter defibrillator; LQT1, Long QT type 1; LQT3, Long QT type 3; PVCs, Premature ventricular complexes; WT, Wild-type; KCNQ1, Potassium voltage-gated channel, type 1; SCN5A, Sodium channel, voltage-gated, type V, alpha subunit.

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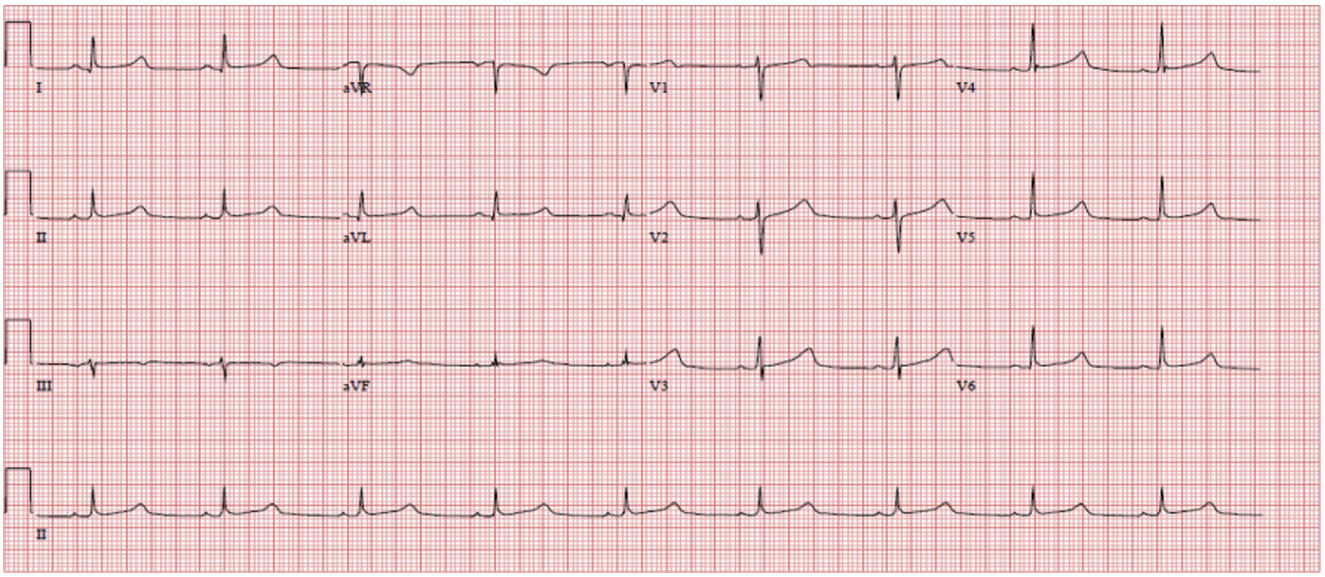

Fig. 1. Resting 12-lead ECG of the proband.

infusion (Fig. 2). There was no occurrence of tachyarrhythmia during the infusion. However, during the washout period (5 min after stopping epinephrine infusion), a gradually prolong R–R interval developed followed by frequent premature ventricular bigeminies preceded by augmented T-U complexes (Fig. 3A). This was followed by non-sustained ventricular tachycardia (VT) (again, the first ventricular tachycardia (VT) beat was preceded by an augmented T–U complex) culminating to persistent polymorphic VT resembling of Torsades de pointes (TdP) (Fig. 3B) which required defibrillation. Given her significant arrhythmias induced by epinephrine, she eventually underwent dual chamber implantable cardioverter defibrillator (ICD) implantation and was placed at lower rate of 70 beats per minute. A year after ICD implantation, she developed polymorphic VT (Fig. 4) treated successfully with an ICD shock which awoken her from sleep.

Subsequent genetic testing of 12 genes known to cause LQTS identified two pathogenic mutations in two different proteins, KCNQ1 (p.R518X) and SCN5A (p.F1617del), causing LQTS type 1 (LQT1) and LQTS type 3 (LQT3), respectively. Further family screening identified that the proband inherited one mutation from each parent (Fig. 5). Her mother carrying the KCNQ1 mutation showed a baseline QTc of 467 ms and significantly prolonged up to a maximum of 516 ms at 0.2 mcg/kg/min epinephrine infusion indicating clinical manifestation of LQTS (Fig. 2). The probands father showed a normal baseline QTc (390 ms) with a maximum QTc of 476 ms at 5 min after stopping epinephrine (Fig. 2). Both children of the proband had borderline QTc intervals of 450 ms and inherited one mutation each as shown in Fig. 4. All first degree relatives of the proband were asymptomatic.

Discussion

This case interestingly illustrates an LQT phenotype with mutations involving both *KCNQ1* and *SCN5A* genes. Accordingly, our

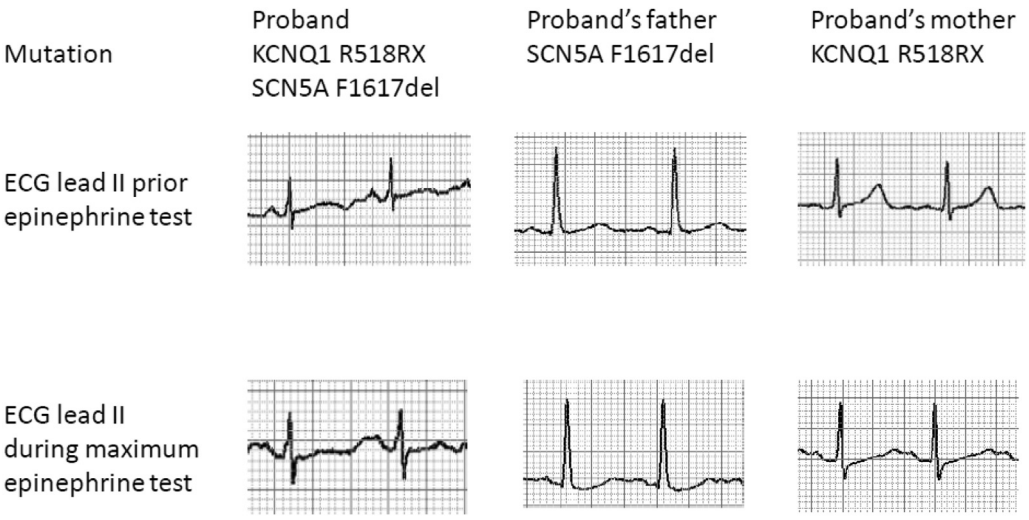

Fig. 2. Comparison of ECGs (lead II) between the proband and her parents before and at maximum epinephrine dosage.