

CASE REPORT

CONGENITAL LQTS – AN ELECTROCARDIOGRAPHIC AND GENOTYPE CORRELATION

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The congenital Long QT Syndrome (LQTS) is characterized by abnormally prolonged ventricular repolarization due to inherited defect in cardiac sodium and potassium channels, which predisposes the patients to syncope, ventricular arrhythmias, and sudden cardiac death. Early diagnosis and preventive treatment are instrumental to prevent sudden cardiac death in patients with the congenital LQTS. The diagnostic criteria for congenital LQTS are based on certain electrocardiographic findings and clinical history. Recently genotype specific electrocardiographic pattern in the congenital LQTS has also been described. Recent studies suggest feasibility of genotype specific treatment of LQTS and, in near future, mutation specific treatment will probably become a novel approach to this potentially fatal syndrome. We describe two cases that fulfilled the electrocardiographic and historical diagnostic criteria with morphology on electrocardiogram (ECG) suggestive of LQT1 genotype.

Keywords: Congenital LQTS, ECG, genotype, pregnancy

INTRODUCTION

The Long QT is a rare congenital disorder characterized by QT-interval prolongation and repetitive episodes of syncope and cardiac arrest related to rapid, polymorphic ventricular tachycardia. Genetic linkage mapping defines six types of LQTS (LQT1-LQT6) out of which, LQT1-LQT3 have been well characterized in clinical studies.¹ Diagnosis of LQTS is based on clinical and electrocardiographic features (table-1)² while T-wave morphology has specifically been shown to be indicator of underlying genotype of LQTS³, being of long duration (broad) in LQT1, small and/or notched in LQT2, and with unusually late onset peaked/biphasic in LQT3⁴ (figure-1).³ Identifying the genotype of LQTS seems to gain importance, as has significant impact on outcome⁵ and management.

These ECG characteristics are useful for selecting which gene to investigate first, while performing genetic analysis. The identification of genotype specific ECG pattern is gaining importance, for its potential use in the management of LQTS, with favorable outcome.

Table-1: Diagnostic criteria for the congenital long QT syndrome

Figure-1. Genotype-specific electrocardiographic (ECG) pattern in the congenital long QT syndrome. Top. The two most common LQT1 ECG patterns: broad-based T-wave pattern (A) and normal-appearing T-wave pattern (B). Middle. The two most frequently encountered LQT2 ECG manifestations: obvious bifid T waves (A) and subtle bifid T wave with a second component on top of the T wave in limb and left precordial leads (B) (or, alternatively, the second component on the down slope of T wave; not shown). Bottom. Most typical LQT3 ECG pattern: late-onset peaked/biphasic T-wave (A). Modified from Zhang et al. *Circulation*. 2000; 102:2849-55 (142), with permission.

The two cases described by us fulfill the diagnostic criteria set in Table-I for LQTS with long duration (broad) T-waves in both cases suggesting underlying genotype to be LQT1.

CASE NO. 1

A 44-year-old lady presented with history of palpitations and a sudden onset syncopal attack. Patient had been experiencing such episodes in the past but was never investigated. Her family and medication history was not significant. The lady was admitted and 12-lead ECG was done which showed a prolonged QT interval (Fig.2a). The corrected QT-interval (QTc) as calculated by applying Bazett formula ($QT\text{-interval} / \text{square root of } RR\text{-interval}$) was 490 msec. Patient was put on telemetry, which recorded multiple runs of polymorphic ventricular tachycardia (torsades de pointes) (Fig-2b). Meanwhile, baseline investigations including routine serum electrolytes and serum magnesium were ordered and 2-D echocardiogram (ECHO) was done. All these investigations were normal. According to the diagnostic criteria in Table-1 patient qualified for the category of definite LQTS as she had a history of syncope of sudden (occurring without stress), a QTc of > 480 msec and recorded runs of torsades de pointes. ECG analysis (Fig-2) for diagnosis of underlying genotype suggested the genotype LQT1 in this case.

Figure 2a. 12-lead ECG showing prolonged QT interval and a brief run of polymorphic VT.

Figure 2b. ECG recorded from Telemetry showing runs of polymorphic VT (Torsades de Pointes)

Patient was started on oral beta-blockers and magnesium supplements with resolution of her symptoms. She was advised to have frequent chemistry check and avoid QT-interval prolonging medications.

CASE NO. 2

A 39-year-old lady, with 20 weeks intrauterine pregnancy, presented with severe episodes of palpitations followed by syncope over a 4 month period. A detailed family and medication history was unrevealing. Patient was admitted and 12-lead ECG was performed which showed ventricular conduction delay and QT-interval prolongation (Fig-3a). The

QTc was calculated (according to Bazette formula) to be of 500 msec. A Holter monitor was placed which revealed frequent monomorphic premature ventricular contractions (PVCs) and non-sustained runs of monomorphic ventricular tachycardia. A single run of polymorphic ventricular tachycardia (Torsades de pointes) was also recorded (fig.3b) coinciding with an episode of syncope. 2-D echocardiogram and routine blood chemistry including serum magnesium were all normal. According to the Table I, history of syncope, QTc of 500 msec and recorded run of torsades de pointes gave the patient more than 4 points and she qualified for the category of definite LQTS. The ECG morphology suggested a genotype of LQT1 when it was compared to the standard ECG shown in Fig-1.

Figure-3a: 12-lead ECG showing prolonged QT-interval and ventricular conduction delay (broad QRS complexes).

Figure-3b: ECG from Holter showing run of polymorphic VT (Torsades de pointes).

While the patient had some pre-pregnancy palpitations, her symptoms had clearly worsened because of the stress of pregnancy. A repeat holter on high dose beta-blockers showed dramatic improvement with complete resolution of monomorphic and polymorphic ventricular tachycardia. Patient later delivered a normal but low-birth weight baby by cesarean section and was discharged on beta-blockers and magnesium supplements. She was advised to have frequent chemistry check and avoid any medicines that may prolong QT-interval. She was placed on magnesium supplements and was advised to have frequent chemistry check and avoid any medicines that may prolong QT-interval.

DISCUSSION

The congenital LQTS is a potentially life threatening condition, caused by mutations in genes encoding cardiac ion channels which result in prolongation of ventricular action potential. Genetic screening of symptomatic patients or their asymptomatic family

members may identify patients at risk for life threatening arrhythmias and the type of LQT as it has important implications in the management. Out of the several forms of congenital LQTS, three forms LQT1, LQT2, and LQT3 have been well characterized. These three forms have also been described on the basis of their specific ECG morphology (Fig-1). Recent investigations suggest that even in patients with acquired LQTS (e.g. resulting from intake of QT-prolonging medicines), there are clinically silent gene mutations that lead to overt QT prolongation only with exposure to QT-prolonging medications.⁶⁻⁸ This explains why some patients seem to be more prone than others to have QT prolongation at a given dose of QT-Prolonging drugs, even after adjustment for other factors that could prolong QT-interval.

The cases reported by us illustrate the fulfillment of criteria for diagnosis of definite LQTS, having both electrocardiographic and historical features and suggest an underlying genotype LQT1 on the basis of ECG morphology. Both the cases had QTc of > 480 msec (fig.2a, 3a), with recorded runs of Torsades de pointes (fig.2b, 3b) and history of syncope. Although ventricular conduction defect is noted in 12-lead ECG of case no.2, there is no standard method to measure the QT-interval in such setting. According to Pfizer Tikosyn program, the QTc should be no more than 500 msec in the presence of ventricular conduction abnormality.⁹ This guidance may be used until a standard method is established for the measurement. Pregnancy adds to the risk of cardiac events during post-partum period in patients with congenital LQTS.¹⁰ Treatment with beta-blockers can reduce this risk. The patient described in case no. 2 was started on oral metoprolol and she showed remarkable improvement in her symptoms with an event free peri and post-partum period.

The clinical course of the congenital LQTS is influenced largely by the gene affected.¹¹ While cardiac events are more frequent and occur at a younger age in patients with LQT1 and LQT2, they are potentially more fatal in patients with genotype LQT3. Patients with LQT1 and LQT2 genotype typically benefit from high dose beta-blocker therapy.^{12,13} However, patients with LQT3 are at higher risk at lower heart rates and potentially may benefit from pace maker therapy. In addition, they shorten their QT-interval more with sodium channel blockers.¹⁴

Facilities for genetic analysis are not easily available in Pakistan. However, in view of the growing importance of genotype specific treatment of this potentially fatal syndrome, one can utilize the ECG criteria as a reliable indicator of the underlying genotype and accordingly tailor the management.

Acknowledgement

We are indebted to G. Michael Vincent for giving us the permission to use figures from his article "ECG findings Identify Genotypes" *Circulation* 2000;102:2849.

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