Long-QT syndrome in a family with a KCNH2 mutation

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Abstract

Long-QT syndrome (LQTS) is an inherited ion channelopathy resulting in abnormal ventricular repolarization and abnormal prolongation of the QT interval on the electrocardiogram. Clinical features vary, from asymptomatic individuals to those with presyncope, life threatening ventricular arrhythmias and sudden cardiac death (SCD). This case report describes a family with a mutation of the KCNH2 gene expressed phenotypically as LQT2 syndrome. The variability in phenotypic expression, the importance of family and genetic screening, and the difficult dilemma of deciding which individuals with LQTS should receive an ICD are discussed.

Keywords: Implantable cardioverter-defibrillator, KCNH2, long-QT syndrome, torsades de pointes

Case report

Ms X was diagnosed with epilepsy as a teenager and for years had recurrent blackouts diagnosed as seizures. In her 40s, the episodes became more frequent and the differential diagnosis of cardiac syncope was raised. An electrocardiogram (ECG) showed her QT interval corrected for heart rate (QTc) to be at the upper limit of normal. Holter monitoring was normal and she opted not to have an implantable loop recorder.

One year later, her older sister, Ms Y, suffered a cardiac arrest. Recurrent torsades de pointes ventricular tachycardia was documented and her ECG revealed abnormal prolongation of the QTc interval. She was diagnosed with long-QT syndrome (LQTS) and an implantable cardioverter-defibrillator (ICD) was implanted for secondary prevention. She was placed on prophylactic β-Blocker therapy.

Given the inherited nature of LQTS, ECG screening was performed in the family. The ECG of Ms X now showed a clearly prolonged QTc interval of 560 ms (Figure 1a). She too was diagnosed with LQTS and only 1 week later presented with recurrent syncope and torsades de pointes ventricular tachycardia (Figure 1b). Like her sister, an ICD was implanted. The ECG of child A (a niece of Ms X) revealed a QTc interval at the upper limit of normal, but with clearly abnormal T-wave morphology (Figure 1c).

Family genetic screening for long-QT gene mutations revealed that several members were found to have a heterozygous mutation of the potassium channel subunit gene, KCNH2 (also known as the human ether-a-go-go-related gene [HERG]), on chromosome 7 (Figure 2). KCNH2 mutations are phenotypically expressed as LQT2 syndrome. The mutation, c.2306T>G (p.L769R), had not been reported previously. It was predicted to result in the non synonymous substitution of a conserved amino acid, indicating a high likelihood that it was a pathogenic variant.

Phenotypic expression within the family varied; with three sisters experiencing syncope and ventricular arrhythmia (Ms X, Ms Y, and Ms Z) while the children carrying the mutation were asymptomatic. Child A had reported infrequent dizzy spells characteristic of vasovagal episodes which improved with β-blockers.
Discussion

Long-QT syndrome

Long-QT syndrome is a rare inherited genetic disorder caused by mutations in cardiac potassium or sodium ion channel genes [1–3]. Reductions in the effective repolarising currents of these defective ion channels lead to prolonged ventricular repolarisation and a susceptibility to ventricular arrhythmias and sudden cardiac death. The ECG QTc interval, representing activation and recovery duration of the ventricular myocardium, is abnormally prolonged.

Genetics

Most LQTS mutations have a heterogeneous autosomal dominant pattern of inheritance, with an estimated prevalence of around 1 : 10 000 of the population. Hundreds of mutations in eight genes (LQTS 1–8), have been identified to date [4]. LQTS 1–3 account for 95% of known mutations, with each syndrome exhibiting different genetic and clinical characteristics (Table I). Clinical presentation of long-QT syndrome can vary significantly due to the different genotypes and variable penetrance. Affected families tend to have their own novel or "private" mutations. Transmission is not strictly Mendelian with an excess of female carriers among the offspring of mutation carriers.

The LQT2 gene, KCNH2, is located on the long (q) arm of chromosome 7 and encodes the pore-forming subunit of the potassium channel. The mutation results in diminution of the repolarising rectifying potassium current (IKr) with abnormal ventricular repolarisation [5]. Over 200 mutations in the KCNH2 gene have been identified.

Clinical features and diagnosis

LQTS carriers may be identified because of symptoms, incidentally, or during family screening. Most mutation carriers remain asymptomatic throughout life, hence clinical disease is less common than the mutation rate. LQTS is identified by abnormal prolongation of the QT interval on the ECG. Normal upper limits of the QTc interval are <460 ms for women and <450 ms for men. However, highly variable disease expression means that such screening tests such as have a sensitivity less than 100%. Indeed, mutation carriers may have normal ECGs or dynamic QTc intervals as illustrated in the case of Ms X, whose QTc interval was initially normal. Causes of acquired prolongation of the QT interval should be excluded before a diagnosis of LQTS is made.

There is a spectrum of clinical manifestations in LQTS from presyncope to syncope from ventricular arrhythmias and sudden cardiac death. The classic...
Arrhythmia is Torsade de pointes ventricular tachycardia. The mean age for first manifestation of the disease is 12 years, but there is a wide range, from the first year of life to as late as the fifth and sixth decades. Sudden death and syncope are uncommon in patients older than 40 years. Arrhythmias may be elicited by stress and emotion or may occur at rest or during sleep [6]. In LQT2 syndrome, sudden loud noises or startle such as an alarm clock, may trigger arrhythmic events. To assist diagnosis, clinical criteria such as the Schwartz scoring system have been developed to determine the probability of having LQTS, encompassing symptoms, family history, and the QTc interval amongst other features [7]. Additional ECG abnormalities such as abnormal T wave morphology are common. Wide-based T waves are most frequently seen in LQT1 whereas notched T waves are most commonly seen in LQT2. The diagnosis of LQTS may only be apparent after provocation tests such as treadmill testing which may yield an abnormal QTc response to exercise [8].

Risk stratification

The QTc interval is the strongest predictor of risk for cardiac events, with an interval exceeding 500 ms carrying a greater than 50% risk of an event before the age of 40 years. Other high-risk features include previous cardiac arrest, symptoms despite adherence to adequate β-blockade, symptoms before puberty, recurrent syncope believed to be caused by arrhythmias, male sex in LQT3 carriers irrespective of QT interval, or onset of syncope with noise or rest [9]. A family history of sudden cardiac death or the proband’s severity of symptoms do not appear to predict severity in other genetically affected family members. The location of the altered amino acid(s) within the ion channel may also affect prognosis, LQT2 carriers with mutations in the pore region are at increased risk for cardiac events compared with non-pore mutations [10].

Genetic and family screening

As an inheritable channelopathy, family screening in LQTS is clearly important. Identification of the typical diagnostic ECG and clinical features described above remains the main screening tool. Although LQTS is a clinical diagnosis, genetic testing for the more common types of LQTS has now become available, and can identify a mutation in 50–75% of probands in whom the diagnosis appears to be clinically certain. Genetic confirmation of LQTS is important both for risk stratification of the proband and for identifying mutation carriers within the family. Once identified, silent carriers of LQTS may be prophylactically treated with β-blockers and receive genetic counselling.

### Table 1. Common forms of long-QT syndrome: genetic and clinical characteristics.

<table>
<thead>
<tr>
<th>Type of LQTS</th>
<th>Disease-associated gene</th>
<th>In vitro effect</th>
<th>Resting ECG</th>
<th>Arhythmia precipitants</th>
<th>ECG at onset of arrhythmia</th>
<th>Clinical response to β-blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>KCNQ1</td>
<td>Decreased Iks</td>
<td>Broad T wave</td>
<td>Physical or emotional stress, swimming</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LQT2</td>
<td>KCNH2 (HERG)</td>
<td>Decreased Ik1r</td>
<td>Low-amplitude T wave, bifid/notched T wave, physical or emotional stress, rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LQT3</td>
<td>SCN5A</td>
<td>Decreased I Na</td>
<td>Long isoelectric ST segment, bradycardia</td>
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ECG, electrocardiogram; LQT, long QT.

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negative guidance test does not, however, exclude the diagnosis, as non-coding variants or unidentified disease-associated genes will result in non-detection. False positive results are also possible since detection of a previously undescribed mutation does not establish a LQTS diagnosis and DNA variants of little significance are well recognised.

**Treatment**

Therapy for LQTS is directed toward reduction of the incidence of syncope and sudden death. The lack of randomized trials of treatment in LQTS reflects both the rarity of the disease and the heterogeneity of its clinical presentations. The data to guide management comes from large registries and referral centers with a bias toward patients with severe disease. Current therapeutic options involve the use of β-blockers and ICDs. Because of adrenergic triggering, affected individuals are also recommended to restrict their participation in athletic activities.

Prophylactic treatment with β-blockers has been shown to be effective in significantly reducing the risk of cardiac events and decreasing the death rate in LQTS [11]. β-Blockers have minimal effect on the QTc interval, but exert a protective effect by reducing the adrenergic stress that classically precipitates arrhythmias in LQTS. Long acting agents are recommended as first line treatment in all affected individuals, with efficacy assessed by the blunting of the exercise heart rate. They are effective in preventing cardiac events in approximately 70% of patients and thus do not provide absolute protection against fatal cardiac arrhythmias. Effectiveness in LQT3 syndrome is less clear than for LQT1 and LQT2.

Implantation of an ICD is indicated for LQTS carriers at high risk of sudden death. The pacemaker function is also used in those with pause-dependent or bradycardia-induced ventricular tachycardia. An important clinical dilemma has been deciding with certainty who should or should not have a defibrillator. The American College of Cardiology/American Heart Association/European Society of Cardiology have issued guidelines, which include the use of ICDs, for the management of LQTS [12]. Prophylactic β-blockade has a Class I indication for all individuals with abnormal prolongation of the QT interval, regardless of symptoms. ICDs have a Class I indication in secondary prevention for those surviving cardiac arrest, Class IIa for those with symptoms or syncope while taking β-blockers, and Class IIb for primary prevention in those with possible high-risk characteristics. Thus, ICD indications for secondary prevention in LQTS are clear but their use in primary prevention is more controversial and debated. One approach would be to implant an ICD for primary prevention in all patients with LQTS, given the risk of sudden cardiac death. In contrast, ICDs are typically implanted in young patients with LQTS, who will have the device for decades, with the significant risks of component failure or infection. Clinical judgment and risk assessment must prevail while outcomes of ICD use in primary prevention are pending.

**Conclusion**

Although a rare congenital disorder, LQTS can have devastating consequences, ranging from syncope to sudden cardiac death. β-Blockers and ICDs are the mainstay of treatment. A more detailed knowledge of the risks conferred by different genetic mutations, and long-term follow-up studies of patients receiving ICDs for primary prevention, will help further to inform decision making in the management of this syndrome.

**REFERENCES**