Long QT Syndrome Revisited
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Abstract
Congenital Long QT Syndrome (cLQTS) is an inherited disease in children and adolescents who have structural normal hearts but present with sudden death in a high proportion of untreated patients. More than 300 mutations have been identified in 7 LQT genes. Diagnosis still depends on ECG, clinical presentations and family history. Molecular genetic testing is useful to unravel borderline family members of LQT probands, but it continues to be a research tool at present. Beta blockers remain the mainstay of treatment. ICDs are highly effective in reducing SCD for high risk patients. Gene based therapy is still preliminary. Considerable thought is needed to address and treat the asymptomatic LQT family members. The main cause of Acquired LQTS is inhibition of Ikr current, usually by drugs. Care must be taken to avoid further exposure to QT prolonging drugs or conditions. Physicians need to be aware of the pharmacodynamic and pharmacokinetic interactions of various important drugs.

INTRODUCTION

1. Congenital Long QT Syndrome (cLQTS) was first described in 1957 in a family in which several children with prolonged QT interval and congenital bilateral neural deafness and syncopal episodes died suddenly, with a family pattern suggesting autosomal recessive inheritance (Jervell and Lange-Nielsen syndrome).
2. A similar but more common familial disorder with QT prolongation but without deafness was described in the early 1960s, with a family pattern of autosomal dominant inheritance (Romano-Ward syndrome) involving QT interval prolongation, syncope and sudden death but without deafness.
3. Traditionally, LQTS is divided into congenital LQTS (c-LQTS) and acquired LQTS (a-LQTS) forms. Drug-induced LQTS is one form of Acquired LQTS. c-LQTS has been thought of as “idiopathic” or due to “sympathetic imbalance” for 3 decades. Over the past 15 years, it has been discovered that c-LQTS is an ion channel disease (“ion channelopathy”).

CONGENITAL LQTS (c-LQTS)

Epidemiology
1. For R-W syndrome, the prevalence is approximately 1 in 5000 to 10000 persons. Higher prevalence is seen in certain areas such as Utah (USA) and Finland (1 in 5000).
2. J-LN syndrome is much rarer, with estimated prevalence of 1.6 – 6 per million in children aged 4 to 15 years.
3. LQTS is associated with a high mortality rate, which can be as high as 70% in untreated patients in 10 years.
Clinical Presentation
1. The age at presentation of c-LQTS varies from in utero to adulthood. Patients may present at a young age with a history of abrupt, exertion-triggered or auditive stimuli triggered syncopoe.
2. Not uncommonly, patients of c-LQTS have been misdiagnosed and treated for epilepsy.
3. A family history of sudden death may be present. Approximately 5–10% of the time the sentinel event of c-LQTS involves sudden death or aborted cardiac arrest. The frequency of these attacks varies from once or twice in a lifetime to once to twice per week.

Genetics and Molecular Mechanisms
1. Mutations causing c-LQTS have been identified in 7 genes (LQT1 to 7, named in order of discovery) in 6 chromosomes, accounting for more than 60% of patients who are affected (Table 1).
2. Currently more than 300 mutations have been identified in an ever growing list. Most (72%) are missense mutations, leading to a single amino acid substitution. LQT1 and LQT2 are the most common mutations.

Electrophysiological Mechanisms
The action potential (AP) in cardiomyocytes is distinctive in its duration (approximately 300 ms) in contrast to that from neurons and skeletal muscle (a few milliseconds). Either the “loss-of-function” or “gain-of-function” abnormality in the K and Na ionic channels prolongs the APD. This is reflected as prolongation of QT interval on the electrocardiogram.

A. Prolonged QTc interval
1. The hallmark of patients with c-LQTS is prolongation of QTc interval, however there is considerable debate as to how and where to measure the QT interval on the ECG. Recent expert guidelines suggest that QT interval should be measured manually in one of the limb leads (usually lead II) from the beginning of the QRS complex to the end of the T wave and averaged over 3 to 5 beats. U waves should be included in the measurement if they are large enough to merge with the T wave.
2. Bazett correction formula (QTc = QT X RR 2/3 ) is still the most widely used method for measuring QTc, although it has been criticized for being inaccurate at fast heart rates (>90 bpm).
3. QTc interval longer than 440 ms has been considered prolonged. However, data from the International Registry for LQTS showed that 68 /1345 family members (5%) who have a QTc<440 ms had a cardiac arrest. Also, only 70% of gene carriers have a prolonged QTc. The others have reduced penetrance: 30% with a QTc< 460 ms and 12% with a QTc<440 ms. Thus, there is considerable overlap.
4. Importantly, none of affected gene carriers had a QTc of 410 ms or less. No normal person had a QTc of 470 ms or more in males and 480 ms or more in females.
5. **Repeat ECGs** are necessary to identify carriers if suspicion is high. A normal QTc or T wave morphology does not exclude LQTS.

6. In atrial fibrillation, QTc intervals after the longest and the shortest RR should be obtained and averaged. QTc and T wave morphology after the longer RR intervals, especially which follow the first sinus beat after AF termination should be carefully examined for T wave alternans and/or PVC.

7. In presence of wide QRS complex, a QTc more than 500 ms is considered prolonged.

8. In the normal population, females have longer QT intervals, probably as a result of QT shortening in males after puberty. In LQTS, men exhibit shorter mean QTc values than both women and children.

**B. ST-T morphology**

1. Patients with LQTS could present with different patterns of ST-T morphologies. As a broad guideline, T wave duration is long in patients with LQTS1 (Fig. 1). Small and/or notched T waves are seen in LQTS2 patients (Fig. 2). T wave onset is unusually prolonged in patients with LQTS3 (Fig. 3).

2. Up to 10 typical ST-T patterns have been described (4 in LQTS1, 4 in LQTS2 and 2 in LQTS3). These patterns were useful in prediction of genotype with a sensitivity of 83-85% and a specificity of 70-94%.

3. A notched T wave during recovery phase of an exercise test is reportedly suggestive of LQTS. **Beat-to-beat alternation of T-wave polarity or amplitude (T wave alternans)** could herald TDP and is a marker for high-risk patients (Fig. 4).

**C. Torsades de Pointes (TDP)**

1. TDP starts with a PVC, followed by a compensatory pause, and then a sinus beat with a markedly prolonged QT interval and an even more bizarre T wave. This is then followed by a train of polymorphic ventricular tachycardia (TDP). The first beat represents triggering from an **Early After Depolarization (EAD)**.

2. It is unknown why TDP reverts spontaneously to sinus rhythm in most instances but degenerates to ventricular fibrillation in others.

**D. Other ECG abnormalities**

1. **QTc dispersion over a temporal frame** (24 hour Holter recording) is an important finding in subtle cases.

2. **Average resting heart rate is lower** in LQTS patients, especially in children. Mean HR is lower than normal control during moderate and maximal exercise in LQTS patients compared to normal controls. Higher incidence of Sinus node dysfunction is also reported.

**Symptoms**

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**Table 1: Genetics of Long OT Syndrome (LQTS)**

<table>
<thead>
<tr>
<th>LQTS Type</th>
<th>Gene</th>
<th>Chromosome Locus</th>
<th>Ion Channel</th>
<th>Effects</th>
<th>Percent of LQTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal-dominant (Romano-Ward)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LQT1 (1991)</td>
<td>KCNQ1 (KVLQT1)</td>
<td>11p15.5</td>
<td>α-subunit of /__ks_ks</td>
<td>↓/_{KS}</td>
<td>50%</td>
</tr>
<tr>
<td>LQT2 (1994)</td>
<td>KCNH2 (HERG)</td>
<td>7q35-36</td>
<td>α-subunit of /__ks_ks</td>
<td>↓/_{KS}</td>
<td>45%</td>
</tr>
<tr>
<td>LQT3 (1994)</td>
<td>SCN5A</td>
<td>3p21-24</td>
<td>α-subunit of /__Na_Na</td>
<td>↑/_{NA}</td>
<td>3-4%</td>
</tr>
<tr>
<td>LQT5 (1997)</td>
<td>KCNE1 (minK)</td>
<td>21q22.1-22.2</td>
<td>β-subunit of /__ks_ks</td>
<td>↓/_{KS}</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>LQT6 (1999)</td>
<td>KCNE2 (MiRP1)</td>
<td>21q22.1-22.2</td>
<td>β-subunit of /__ks_ks</td>
<td>↓/_{KS}</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>LQT7 (2001)</td>
<td>KCNJ2</td>
<td>17q23</td>
<td>/kir2.1</td>
<td></td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

| Autosomal-recessive (Jervell and Lange-Nielsen) |
|-----------------------------------|---------------|-----------------|-------------|---------|-----------------|
| JLN1 (1997)                       | KCNQ1 (KVLQT1)| 11p15.5         | α-subunit of /\_\_ks\_ks      | ↓/_{KS} | <1%             |
| JLN2 (1997)                       | KCNE1 (minK)  | 21q22.1-22.2    | β-subunit of /\_\_ks\_ks      | ↓/_{KS} | <1%             |
the age of 40. Approximately 30% of the carriers never have any symptoms. In men, the risk for the first cardiac event is higher in childhood and decreases after puberty.

3. Approximately 75% of all pts (almost all LQT1 / LQT5 and 50% of LQT2 / LQT6) have events precipitated by adrenergic stimuli.

4. Pts with LQT1 have a high frequency of cardiac events associated with vigorous physical activities, especially diving and swimming.

5. Pts with LQT2 are particularly sensitive to arousal-type emotions such as sudden loud noise by ringing of an alarm clock or telephone.

6. LQT3 pts experience events without emotional arousal during sleep or at rest.

Diagnosis
1. Clinical suspicion is of pivotal importance in the diagnosis of LQTS. A typical presentation is that of a child or young adult experienced an unexplained syncope or SCD during physical exertion or emotional agitation, or suffered from a history of drowning or near-drowning.

2. Diagnostic criteria are based on findings from the ECG, clinical history and family history (Table 2). In pts with intermediate probability, serial ECGs are important because QTc value in pts could vary with time.

3. Molecular genetic testing remains primarily a research tool and is not available from routine screening. Moreover, it is successful in only 60-70% of clinically affected pts.

Risk Stratification
1. A recent study of 647 pts from 193 consecutively genotyped families with LQTS showed that the risk of first cardiac event (syncope, cardiac arrest and SCD) before the age of 40 yrs and before therapy can be stratified by genotype, sex and the length of the QT interval.

Prognosis and therapeutic strategies
1. In untreated symptomatic LQTS pts, mortality rates exceed 20% in the year after the first syncopal attack, and the averaged annual risk of syncope is 5%. The overall mortality in 10 yrs is 50%.

2. In symptomatic patients, Beta blockers, Cardiac Pacing, Left cardiac sympathetic denervation (LCSD) and Implantable Cardioverter Defibrillator (ICD) markedly improve survival and reduce the 5-year mortality to 3 – 5%.

3. In asymptomatic patients, devising a therapeutic strategy is a topic of continuing debate. Treatment is recommended in pts with J-LN syndrome; in neonates and infants; in affects siblings of children who have had SCD; in pts with documented T wave alternans; in pts with a very long QTc (> 600 ms); and on explicit request for treatment by the family.

Table 2: Diagnostic criteria in Long QT syndrome (LQTS)37

<table>
<thead>
<tr>
<th>Electrocardiographic findings*</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>&gt; 480 ms</td>
<td>3</td>
</tr>
<tr>
<td>460-470 ms</td>
<td>2</td>
</tr>
<tr>
<td>450 (male) ms</td>
<td>1</td>
</tr>
<tr>
<td>Torsade de pointes&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td>T-wave alternans</td>
<td>1</td>
</tr>
<tr>
<td>Notched T-wave in 3 leads</td>
<td>0.5</td>
</tr>
<tr>
<td>Low heart rate for age&lt;sup&gt;§&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Clinical history</td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>2</td>
</tr>
<tr>
<td>With stress</td>
<td></td>
</tr>
<tr>
<td>Without stress</td>
<td>1</td>
</tr>
<tr>
<td>Congenital deafness</td>
<td>0.5</td>
</tr>
<tr>
<td>Family history&lt;sup&gt;†&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Family members with definite LQTS&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>1</td>
</tr>
<tr>
<td>Unexplained-sudden cardiac death</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Before age 30 among immediate family members

Scoring: <1 point = low probability; 2-3 points = intermediate probability >4 points = high probability.

Modified from reference 37 with permission.

*In the absence of medications or disorders known to affect these electrocardiographic features.

†QTc calculated by Bazett's formula, where QTc = QT x RR<sup>½</sup>

‡Mutually exclusive.

§Resting heart rate below the second percentile for age.

#The same family member cannot be counted twice.

†Definite LQTS is defined by an LQT score >4.

1. βB remain the mainstay of therapy because 75% of the cardiac events are precipitated by adrenergic stimuli. They decrease the mortality from 71% in historical controls to 6% in a treated group.

2. Syncope or other events recur in pts on βB in approximately 25% of cases, and the chance of SCD at 5 yrs has been estimated to be 10% despite therapy.

3. Maximal β-blockade is recommended, assessed by a maximal HR less than 130 bpm. Propranolol at 2 – 3 mg/kg/day or Nadolol at 1 mg/kg/day is widely used (in the West).

B. Cardiac Pacing
1. In pts who develop severe bradycardia, concomitant pacemaker therapy is indicated. It is also recommended in pts with AV block and in pts with LQT3.

2. The pacemaker should be programmed to a high lower rate limit (>80 bpm) and pause-prevention algorithm.

C. Left Cardiac Sympathetic Denervation:
1. LCSD is recommended in pts who are resistant to βB, and has shown remarkable benefit. Thoracoscopic sympathectomy has short operative time and minimal complications.

D. ICD
1. International LQT Registry has revealed that Pts who received ICD have a total mortality of 1.3% over 3 years compared with 14% in the non-ICD patients over 8 years.

2. ICD is suggested to be used in high-risk symptomatic pts or in pts in whom the combination of βB, LCSD and/or pacing fails to prevent syncopal attacks. It is also proposed as first-line therapy when the presenting event is a resuscitated cardiac arrest.

E. Gene-based specific therapy
1. Nikorandil, an ATP-sensitive K channel opener may be of benefit is pts with LQT1 and LQT2 by shortening the prolonged QT and
reducing transmural dispersion.

2. R-L3, a benzodiazepine is an Ikr activator. It shortens the APD and suppresses EADs in ventricular myocytes. This drug has promise for the future, but is still under study.

F. Lifestyle modification
1. Pts with LQT1 should avoid strenuous or competitive exercise, especially swimming and diving.
2. Pts with LQT2 should be protected from sources of loud noise (by removing alarm clocks and telephones from there rooms).
3. LQT pts should have a disease identification card on person at all times. They should consult their doctor before taking any medication.

ACQUIRED LQTS

Etiology and Pathophysiology
1. The hallmark mechanism of drug-induced LQTS and TDP is the blockade of Ikr, a major repolarization current in the heart. A number of drugs are capable of doing this. Cytochrome P450 (CYP450) 3A is responsible for the metabolism of the largest number of drugs followed by CYP2D6.
2. The risk of developing TDP correlates with the degree of prolongation of QTc interval as shown in the following equation: Risk = 1.052^X, where X is a 10 ms increase in QTc interval. Thus, the risk of TDP in a pt with a QTc of 600 ms is almost triple that in a pt with a QTc of 400ms.

Treatment
When polymorphic VT is encountered, the first step is to examine the QTc interval immediately before or after the tachycardia to see if it is prolonged. If QTc is prolonged:
1. Review the drug history thoroughly.
2. Discontinue all QT prolonging drugs.
3. Suppression of EADs by IV MgSO4: 2 gm bolus followed by
4. Shortening of QTc by IV KCl, IV Lidocaine and by increasing ventricular rate. This can be done by IV Isoproterenol infusion or Cardiac pacing (120 – 140 bpm).
5. After stabilization, check for possibility of congenital LQTS by analyzing previous ECGs, personal and family history. The therapy will need to be tailored to the patient depending on whether the etiology is cLQTS or aLQTS precipitate by drugs.

SUMMARY
LQTS is a unique disease because it is a paradigm of genetic mutation affecting ionic channels (ion channelopathy) resulting in electrical repolarization abnormalities in the cardiomyocytes. Although rare, a high index of suspicion is required to diagnose and manage the cLQTS variety. Acquired LQTS is encountered more frequently. A continuous update of our knowledge of drug metabolism is necessary to prevent, identify and treat this problem.

REFERENCE