The Long QT Syndrome: problem identification, diagnostic challenges

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Abstract

The Long QT syndrome (LQTS) is inherited or acquired channelopathy resulting ventricular tachyarrhythmia torsade de pointes (TdP) which causes syncope and sudden death. The acquired LQTS might be drug-induced that is significant public health issue. The estimated prevalence of inherited LQTS in the USA is estimated at about 1:7000 or 1: 5000 individuals according to different sources. The article covers the most important issues of the syndrome, clinical and diagnostic challenges when QT interval prolongation is seen on ECG in order to assist doctors deal with the problem.

LQTS is caused by mutations of genes which encode for cardiac ion channels. Five genes, (LQT1,2,3,5,6) with over 200 mutations have thus far been discovered. Clinically, LQTS is identified by abnormal QT interval prolongation on the ECG. Genotype-phenotype studies of LQTS have provided new insights into risk mechanisms, electrocardiographic features, and long-term clinical course associated with this inherited disorder. Individuals with LQTS are practically healthy people without structural problems of the heart. The first manifestation of the disorder may be a fainting episode or syncope and sudden cardiac death. These events are due to the ventricular tachyarrhythmia torsade de pointes (TdP). ECG is informative and practically the main tool for diagnosis. The characteristic signs are QT interval prolongation and T wave abnormalities. Usually, the rate adjusted QT interval is calculated (QTc) using the Bazett formula (QTc = QT/√RR). In case of suspicion, the QTc ranges from about 410 to over 600 msec. The most difficult task is to assess the risk of further arrhythmic events. Several approaches are implemented in clinical practice with this purpose (Schwartz score, Priory criteria). Management of LQTS includes mainly beta-blockers, education of patients to avoid triggers, pacemakers in case of bradycardia or ICDs. (TCM-GMJ October 2018; 3(2):P12-P14)

Keywords: Long QT Syndrome; Torsades de pointes; New insights of LQTS

Introduction

Long QT syndrome (LQTS) is inherited or acquired channelopathy resulting ventricular tachyarrhythmia torsade de pointes (TdP) which causes syncope and sudden death. The acquired LQTS might be drug-induced that is significant public health issue. The estimated prevalence of inherited LQTS in the USA is estimated at about 1:7000 or 1: 5000 individuals according to different sources. However, because of diagnostic challenges and variable genetic mutations, the prevalence of patents with overt or subclinical manifestations of the syndrome is likely to be considerably greater than estimated prevalence (1).

The definitive description of LQTS occurred in 1957. Anton Jervell and Fred Lange-Nielsen described a Norwegian family in which 4 of 10 children were deaf and had recurrent syncope during exercise or emotion (2). Three died suddenly, at ages 4, 5 and 9 years. QT prolongation on the ECG was dramatic. Inheritance appeared to be autosomal recessive. A similar clinical syndrome of sudden death during exercise and emotion, but with normal hearing and autosomal dominant inheritance, was described in 1963 by Romano, et al, and in 1964 by Ward (2,3).

These two forms of inherited LQTS have respectively known as the Jervell, Lange-Nielsen (J, L-N) and the Romano-Ward (R-W) syndromes.
Genetics and Molecular basis

LQTS is caused by mutations of genes which encode for cardiac ion channels. Five genes, (LQT1,2,3,5,6) with over 200 mutations have thus far been discovered (4). Using published genotype information, phenotype analysis by ECG findings, and event triggers of patients from centers around the world, it appears that about 95% of LQTS cases are caused by mutations of the potassium genes. The LQT1/LQT5 combination appears to account for about 60%, LQT2/LQT6 about 35%, with mutations of LQT5 and LQT6 alone contributing about 1% each to these numbers. The sodium channel gene LQT3 accounts for about 4-5% of the cases, and Jervell, Lange-Nielsen less than 1%. The LQT4 genotype is very rare and may be present in only the proband family, as no other families with genotype have been described (5). During the past few years, mutations in other genes have been identified in single individuals or a few families in what can be categorized as “LQTS related” disorders.

Clinically, LQTS is identified by abnormal QT interval prolongation on the ECG. Genotype-phenotype studies of LQTS have provided new insights into risk mechanisms, electrocardiographic features, and long-term clinical course associated with this inherited disorder. For example, each of the 3 major genotypes (LQT1 to LQT3) seems to have a distinctive T-wave repolarization pattern on the ECG (figure 1) (5,6).

Clinical Manifestations

Individuals with LQTS are practically healthy people without structural problems of the heart. The first manifestation of the disorder may be a fainting episode or syncope and sudden cardiac death. These events are due to the ventricular tachyarrhythmia torsade de points (Tdp), (Figure 2). Most often, the Tdp is self-terminating producing a syncopal episode. In a small minority of events the Tdp degenerates into ventricular fibrillation and death occurs.

Syncope might be the first presentation of the disease in LQTS patients. The precise analysis of the syncope history is usually the key to the correct diagnosis. Palpitations and presyncope are uncommon due to LQTS. In LQTS it is precipitous and without warning in the vast majority of cases. Syncope in patients with the long-QT syndrome is generally attributed to the form of polymorphic ventricular tachycardia called torsades de points (Tdp) the usual rate of Tdp is about 300-350/min, and the arrhythmia starts suddenly. The LQT3 form of the syndrome can also be associated with bradycardia, and slow heart rates may cause syncope in some patients. Death is usually due to ventricular fibrillation. The reason is that. No cardiac mechanical function occurs at such fast rates, thus, there is nothing to cause palpitations. A history of palpitations and presyncope is very much more likely to be due to vasovagal physiology, a different cause and type of VT, or SVT. A very careful history usually clarifies the situation. LQTS will be precipitous, as above, no symptoms typical of vasovagal physiology will be present, the event will not be during positional change, often absence of respiration and cyanosis will be detected, and the duration of the syncope is longer than the vasovagal event that is very usually very brief.

At least one-third (7) and probably about one-half of gene carriers never have symptoms, and it is common for the family history to be negative at the time of diagnosis in a member. However, a history of unexplained sudden death or repetitive syncope in young members of a family is certainly suspicious for LQTS.

Diagnosis

ECG is informative and practically the main tool for diagnosis. The characteristic signs are QT interval prolongation and T wave abnormalities. There is significant variability of the QT within members of any family, between families and to a much lesser extent, between genotypes.

ECG diagnosis is based on QT measurements in certain lead (II and V5 or V6 with the longest value used). Usually, the rate adjusted QT interval is calculated (QTC) using the Bazett formula (QTC = QT/√RR). The range of values in a normal population is about 350 to 460 msec. In case of suspicion, the QTC ranges from about 410 to over 600 msec. Consequently, there is overlap of QTC values between LQTs and normal in the 410 to 460 msec range. Values in this range are non-diagnostic and further studies are required.

T wave is further component of ECG to be evaluated. Moss, et al first reported a T wave pattern characteristic for each genotype (8). Zhang, et al further described patterns characteristic for each genotype, reporting four for LQT1, four for LQT2 and two for LQT3 (9). These T patterns can be helpful for predicting the correct genotype in families, and can be of assistance in the diagnosis of LQTs in cases of borderline QT duration.

However, LQTS is not the only cause of the QT prolongation on ECG. There are a number of causes of QT prolongation other than inherited LQTS including electrolyte disturbance, use of QT prolonging medications, mitral valve prolapse, diabetic autonomic neuropathy and cardiomyopathies. These conditions must be excluded when evaluating a patient who has a prolonged QT interval before a confident diagnosis of the Long QT syndrome can be made. Current evidence suggests that in the absence of these confounding factors, a QTc of ≥ 480 msec in females and ≥ 470 msec in males allow the diagnosis of LQTS. QTcs of < 410 msec make LQTS quite unlikely. Values between 410 and 460 msec are ambiguous and further testing must be performed to clarify the status of these patients. That further testing includes additional ECGs, ambulatory ECGs and exercise ECGs. Exercise ECGs seem to be the most definitive. Genetic testing is helpful when available.

The sensitivity/specificity of the screening strategy is not well defined. Commercial genetic testing for de novo mutations is restricted. Commercial genetic testing for members of families with a known mutation is available, with analysis limited to the exon involved. De novo mutation screening is available in some research laboratories.

Importantly, approximately 30% of phenotypically affected subjects have no mutation identified on genetic analysis. They may have mutations of genes not yet recognized. Alternatively, they may have mutations of non-coding regions of the known genes, or regulatory or modifier genes.

Clinical course and Risk Stratification

Regardless of the philed/filed material, the natural history of the syndrome remains incompletely characterized and approaches to risk stratification are not well defined.

In 1985, Schwartz et al published the criteria for diagnosing LQTS, which were modified in 1993 and contain important guidelines for the initial evaluation of potential cases. This system uses a score of 1 to 9 based on the family history, and the clinical and electrocardiographic findings. The probability of disease is low at a score of ≥ 1, intermediate at 2-3, and high at ≥ 4 (Table 1).

One of the most current and definitive data regarding the risk of complications come from the International LQTS regis-
try. Zareba, et al (5) reported on LQTS patients of all three genotypes. The death rate over 40 years was about 4% for each genotype. This finding has tremendous importance for treatment and follow-up strategies in LQTS patients. The rather low incidence of sudden death indicates that we badly need to identify reliable risk markers, not accurately possible at present. With such data, the large majority, who are at low risk, might be stratified to no treatment, whereas those at higher risk could be appropriately managed with aggressive and target driven beta-blocker therapy, ICDs or other genetic based therapies as they become available. Also, the Registry study determined that the frequency of cardiac events (syncope, aborted cardiac arrest and sudden death) was highest in LQT1 (60% of patients), then LQT2 (40%) and lowest in LQT3 (18%). Since the rate of death was the same in each genotype, the percentage of events which were lethal was highest in the LQT3 patients.

According to S.G. Priori, M.D., Peter J. Schwartz, et al, the genetic locus and the QTc, but not sex, were independent predictors of risk after evaluation of 647 patients from 193 consecutively genotyped families with the long-QT syndrome. The QTc was an independent predictor of risk among patients with a mutation at the LQT1 locus and those with a mutation at the LQT2 locus but not among those with a mutation at the LQT3 locus, whereas sex was an independent predictor of events only among those with a mutation at the LQT3 locus. Finally, they suggested a risk-stratification model in order to quantify, for each genetic variant, the risk of symptoms before the age of 40 years and before therapy on the basis of two simple clinical characteristics: sex and QTc (Table 1).

**Therapy**

Management of LQTS includes mainly beta-blockers, education of patients to avoid triggers, pacemakers in case of bradycardia or ICDs. The last one gained more popularity to prevent episodes of syncope due to TdP or avoid sudden cardiac death (SCD). It is indicated to be implanted in patients with high risk or as a secondary prevention of SCD.

**Gap in knowledge of LQT Syndrome**

The natural history of the syndrome remains incompletely characterized; as well as approaches to risk stratification are not well defined.

These gaps in knowledge are largely due to the fact that the long-QT syndrome is uncommon, cardiac events may be separated by long periods without symptoms, and the initial manifestation may occur late in life.

The diagnosis is based on QT measurement or T wave abnormality that is not always diagnostic. QT might be normal during investigation and could mask real mutation carrier. We need more distinctive clinical or diagnostic characteristics not to miss the real.

**Figure 2: Ventricular tachycardia - Torsade de pointes**

**Table 1. Schwartz Score for the diagnosis of Long QT**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiogram</td>
<td>3</td>
</tr>
<tr>
<td>- QTc ms 480</td>
<td>2</td>
</tr>
<tr>
<td>- 450 (males)</td>
<td>1</td>
</tr>
<tr>
<td>- Torsades de pointes</td>
<td>2</td>
</tr>
<tr>
<td>- T wave alternance</td>
<td>1</td>
</tr>
<tr>
<td>- T wave noches in 3 leads</td>
<td>1</td>
</tr>
<tr>
<td>- Bradycardia</td>
<td>0.5</td>
</tr>
<tr>
<td>Clinical history</td>
<td></td>
</tr>
<tr>
<td>- Syncope with stress</td>
<td>2</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</td>
<td></td>
</tr>
<tr>
<td>- Family members with confirmed LQTS</td>
<td>2</td>
</tr>
<tr>
<td>- Unexplained death in first-order family members &lt; 30 years</td>
<td>1</td>
</tr>
</tbody>
</table>

**References**


**Figure 1: Main types of LQTS**