CARDIOLOGY Rounds®

As presented in the rounds of the Division of Cardiology, St. Michael's Hospital, University of Toronto

The Long QT Syndrome

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A Case History

A 27-year-old patient is referred for the assessment of multiple episodes of loss of consciousness. She began to have syncope at about age 19, initially once or twice a year, but 5 times in the past year. A neurologist diagnosed seizure disorder and placed her on anti-seizure drugs. The syncopal episodes usually occur without any warning, leaving her unconscious for a few minutes, but feeling well thereafter. There are no prodromal symptoms whatsoever. On several occasions, she has fainted after hearing a telephone ring or upon being awakened by an alarm clock. What would you do now? What advice would you give her?

Sudden cardiac death (SCD) affects over 300,000 people each year in the US alone,[1] primarily affecting older patients with coronary artery disease (CAD). However, an important minority of these deaths occur due to a treatable and often preventable condition termed the "long QT syndrome" (LQTS). The LQTS is characterized by prolongation of the QT interval on the surface electrocardiograph (ECG), polymorphic ventricular tachycardia, recurrent syncope, and possibly, sudden cardiac death. It can be acquired or familial. The traditional concept that congenital and acquired LQTS are two distinct clinical entities has been challenged by recent links discovered between the two disorders. This issue of *Cardiology Rounds* presents a description of congenital and acquired LQTS and torsades de pointes, and reviews the diagnosis, symptoms, prognosis, and treatment of these clinical entities.

Congenital LQTS

Congenital LQTS is caused by mutations in the genes encoding the cardiac potassium or sodium channel. This results in altered channel function, leading to changes in repolarizing or depolarizing currents, and resulting in prolonged action potential duration and delayed repolarization in myocardial cells. This is reflected on the ECG as a prolonged QT interval, abnormal T waves, and episodic polymorphic ventricular tachycardia occurring often, but not always, in the setting of high adrenergic activity (eg, physical or emotional stress).

Congenital LQTS is a rare disorder affecting 1 in 10,000-15,000 people[2] and it may be responsible for as many as 3,000 unexplained deaths in children and young adults each year in the United States. Often the syndrome has been undiagnosed, thus the frequency with which it occurs is unknown. Inherited long QT syndrome can be caused by 1 of at least 177 mutations or defects in any of 5 cardiac-related genes – and likely more. Genotyping is negative (ie, fails to uncover a known mutation) in one-third to one-half of patients with LQTS, suggesting that there may be many more undiscovered mutations.[2] Patients with familial LQTS often have affected family members, but spontaneous mutations can also occur. The syndrome may have variable or low penetrance, meaning that not all affected relatives will have prolonged QT interval in the surface ECG.

The long QT syndrome is subdivided into genetically distinct subtypes: LQT1 (the most common form), LQT2, LQT3, LQT4, LQT5, and LQT6 (Table 1). Each subtype causes either a reduction in the net outward potassium current or an increased net inward sodium current, both result in prolongation of the action potential duration. Early "after-depolarizations" and enhanced dispersion of refractoriness result in torsade de pointes (TdP), which may be triggered by activity and maintained by reentry mechanisms.

The incidence of acquired LQTS or drug-induced TdP in the general population is difficult to estimate. Knowledge regarding risk factors and incidence is mainly derived from epidemiological studies during the clinical development of drugs or from reported adverse effects after drugs are introduced to

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the market and therefore has serious limitations when used to estimate the incidence in the general population.

Acquired LQTS

Acquired LQTS is much more common than the congenital variant and can occur in up to 3%-5% of patients receiving antiarrhythmic drugs that prolong the QT interval. Such patients may also have some subtle genetic defects rendering them more susceptible to excessive QT prolongation, either by causing a reduction in channel activity or by rendering the channel more sensitive to drugs that can cause prolonged repolarization.[2,3] Slight QT prolongation can be found before drug treatment in 56%-71% of patients who eventually develop drug-induced proarrhythmia, which suggests a pre-existing predisposition.[4] These patients may be considered to have "reduced repolarization reserve" manifesting only with conditions that predispose to QT prolongation (eg, drugs that prolong the action potential duration, hypokalemia, hypomagnesemia, or bradycardia, Table 2).[2] Other clinical conditions associated with an increased risk of acquired LQTS include heart failure, left ventricular hypertrophy (LVH), hypothyroidism, and old age. Because LVH and heart failure are associated with abnormal repolarization, proarrhythmia is more common with class III antiarrhythmic drugs in these conditions.

Importantly, females are several fold more likely to develop acquired LQTS. The mechanism is unknown, but may relate to the shortening of QT interval by androgens or QT lengthening by estrogens. A whole range of commonly used drugs from non-related classes have been shown to prolong cardiac repolarization and potentially cause TdP in susceptible individuals. The underlying mechanism of this adverse effect is a blockade of cardiac potassium channels that may mimic congenital LQTS. Selective blockade of the rapidly activating delayed rectifier potassium channel (I_{Kr}) produces a heterogeneous prolongation of the action potential duration, especially at slow heart rates (reverse use dependence). While modest QT prolongation (<60 ms) is expected with all class III antiarrhythmics, occasionally patients develop profound QT prolongation (>60 ms or to an absolute QT interval value of 550 ms) and TdP. The syndrome can occur in up to 6% of patients receiving sotalol or dofetilide, 4.3% with ibutilide, 1%-8% with quinidine, and 0%-2% with amiodarone.[2]

Table 1: Classification of LQTS according to gene and ion channels involved

Type	Gene	Ion Channel
LQT1	KCNQ1 (KVLQT1)	I_{Ks} (α-subunit)
LQT2	KCNH2 (HERG)	I_{Kr} (α-subunit)
LQT3	SCN5A	I_{Na} (α-subunit)
LQT4	?	?
LQT5	KCNE1 (MinK)	I_{Ks} (ß-subunit)
LQT6	KCNE2 (MiRP1)	I_{Kr} (ß-subunit)

LQT = Long QT
I_{Ks}/I_{Kr} = slowly/rapidly activating rectifier potassium current
I_{Na} = sodium current

Table 2: Causes of acquired LQTS

Factor	Mechanism
Bradycardia	Prolongs APD
Drugs (with class III antiarrhythmic action)	I_{Kr} and I_{Ks} blockade
Hypokalemia, Hypomagnesemia	I_{Kr} blockade and increased I_{Kr} sensitivity to pharmacological blockers
LVH/CHF	Decreased K currents (I_{Kr}, I_{Ks}, I_{to})

APD = action potential duration.
I_{Ks}/I_{Kr} = slowly/rapidly activating component of the potassium current
I_{to} = transient outward current
LVH = left ventricular hypertrophy
CHF= congestive heart failure

Torsade de pointes

Torsade de pointes associated with amiodarone does not generally correlate with the pretreatment QT interval. The exact mechanism behind the low incidence of proarrhythmia with amiodarone is not clear; however, it has been suggested that additional electrophysiological actions with amiodarone (eg, beta-blocking, calcium channel blocking, and sodium channel blocking effects) might reverse the basic electrophysiological abnormality that favours TdP despite the markedly prolonged QT interval that is seen with amiodarone.

Although TdP most often occurs within the first few days of drug initiation, it may also develop during long-term treatment.[5,6] This late occurrence of proarrhythmia has been linked to changes in dose, reinitiation of the drug after a short discontinuation, new bradycardia, or transient hypokalemia or hypomagnesaemia. The proarrhythmia is frequently dose related; however, quinidine-related TdP is considered an idiosyncratic reaction, occurring at low doses (even after a single dose) or at low sub-therapeutic plasma concentrations. This early proarrhythmia with quinidine may be due to a potent unopposed blockade of potassium channels at low concentrations. A concomitant sodium blockade at higher therapeutic levels may alleviate this risk.[2] A common scenario occurs when there are drug interactions (usually involving ≥ 2 drugs) that prolong the QT interval or when 1 drug inhibits the metabolism of a QT-prolonging drug.

An increased risk of TdP has been identified with concomitant use of terfenadine and ketoconazole.[7] Erythromycin or ketoconazole are both inhibitors of liver enzymes and are reported to cause a significant interaction with the metabolism of cisapride and TdP. Cisapride has been removed from the North American market due to this adverse effect. In addition, ketoconazole can also block the potassium channel. Because TdP can be related to drug plasma concentration, alterations in organ function that decrease the systemic clearance of the drug will increase the risk of TdP. For example, sotalol or dofetilide are largely eliminated by the kidneys and these drugs will accumulate if there is renal impairment and

cause excessive risk of TdP unless dose adjustments are made. Cases of TdP after oral clarithromycin in critically-ill patients with hepatic and/or renal impairment have been reported.

ECG risk factors for TdP include baseline QT prolongation, T wave lability and increased QT dispersion.[8] Associated risk factors outlined in Table 1 play an important role in the clinical manifestations of acquired LQTS. This suggests that drug-induced TdP is not a "drug-specific response," but rather a "patient-specific response." Many medications may prolong the QT interval and also trigger serious ventricular arrhythmias including:

- antiarrhythmic drugs (eg, disopyramide and procainamide)
- antihistamines (eg, terfenadine or astemizole)
- antibiotics (eg, azithromycin, clarithromycin, erythromycin, itraconazole, ketoconazole, moxifloxacin, pentamidine, sparfloxacin, sulfamethoxazole-trimethoprim or amantadine)
- antidepressants (eg, amitryptiline, imipramine, or doxepine)
- neuroleptics (eg, haloperidol, risperidone or thioridazine)
- motility agents (eg, cisapride)
- many others.

For a complete list of drugs reported to prolong the QT interval and cause TdP see http://www.qtdrugs.org.

Diagnosis of LQTS

In 1993, diagnostic criteria were published to facilitate the diagnosis of familial LQTS.[9] Scoring was based on ECG findings, clinical history, and family history. Point scoring was divided into 3 probability categories: low, intermediate, and high probability (Table 3). Further studies have shown that this clinical score system is not sufficiently sensitive in genetically-affected patients with normal phenotypes.[10] Generally, the diagnosis is made from the 12-lead ECG and the QT interval should be measured manually from the onset of the QRS complex to the end of the T wave (defined as the intersection of the isoelectric line with the tangent to the maximal slope of the T wave), and not only from the computer evaluation of the ECG.

Table 3: Diagnostic criteria for inherited LQTS[9]

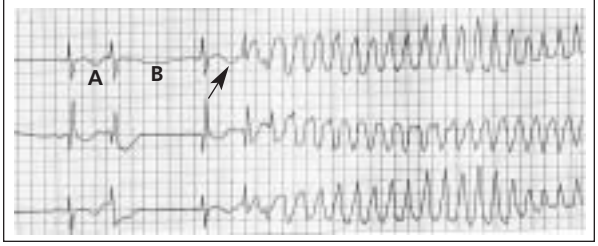
Criterion	Points
QTc > 480 ms	3
QTc: 460-470 ms	2
QTc: 450 ms (male)	1
Torsade de Pointes	2
T wave alternans	1
Notched T wave	1
Low heart rate for age*	0.5
Syncope with stress	2
Syncope without stress	1
Congenital deafness	0.5
Family members with definite LQTS (score >4)	1
Unexplained SCD among immediate family members <30 years old	0.5

* Resting heart rate below the second percentile for age

QTc = corrected QT interval using Bazett's Formula
LQTS = long QT syndrome
SCD = sudden cardiac death

Scoring: < 1 = low probability of LQTS
2 - 3 = intermediate probability of LQTS
> 4 = high probability of LQTS

Figure 1: ECG showing the typical initiating short (A) - long (B) sequence and a large amplitude multiphasic T wave (arrow), preceding polymorphic ventricular tachycardia. Note that the coupling interval from the QRS onset of the last normal beat to the onset of the first beat of tachycardia is long, 600 ms, and occurs before the end of the QT interval.



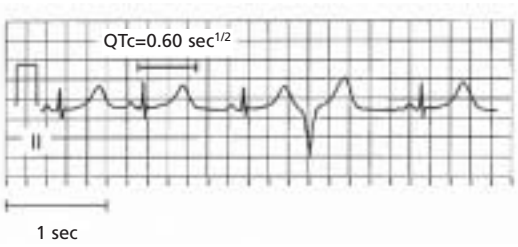
Bazett's formula (QTc = QT divided by the square root of RR interval) has been most frequently used for the heart rate correction of the QT interval. A prolonged QT interval that is diagnostic is present in only 60%-70% of cases. Up to one-third of people with a LQTS gene have a normal QT interval on resting ECG, and ventricular arrhythmia, in a setting of intermittent long QT interval, may be the first presentation of the disease. Screening families with LQTS revealed that up to 45% of affected patients have a normal phenotype (ie, a normal 12-lead ECG), but these patients are still are capable of transmitting the disease (incomplete penetrance).[11]

The hallmark arrhythmia associated with QT prolongation is TdP, which is usually characterized by a typical short-long initiating sequence resulting in polymorphic ventricular tachycardia (Figure 1); QT prolongation may be most prominent or only seen following post-extrasystolic pauses. The first beat of ventricular tachycardia typically interrupts a bizarre large amplitude T wave with a markedly long QT interval.

The relative or absolute bradycardia immediately following reversion of atrial fibrillation to sinus rhythm is also a very vulnerable period. This pattern can be observed regardless of the specific drug provoking the arrhythmia. Because QT abnormalities can be very subtle, it is extremely important that the ECG be analyzed carefully. A QT interval corrected for the heart rate (QTc) >440 ms in males and >450 ms in females is generally considered "abnormal" (Figure 2), although the predictive value associated with this sharp distinction is low.

Alterations in T wave morphology or amplitude are common in both the congenital and acquired variants of LQTS (Figures 3, 4). In addition, a second delayed repolarization wave, distinct from the normal T wave, can often be seen. These may represent U waves or biphasic T waves, and are usually most visible in the lateral and left precordial leads.

Figure 2: Lead II tracing from a 19-year-old woman after a near-drowning that reveals marked prolongation of the QT interval[17]



When only 1 lead is available, separation between the T and U waves is difficult. Changes in the T wave morphology and the occurrence of U waves constitute important warning signs that may precede TdP. When U or biphasic T waves are visible, the arrhythmia usually starts from the peak or the descending portion of the second T wave component or the U wave.

In congenital LQTS, there appears to be a relatively specific genotype-phenotype correlation. Broad-based T waves typify LQT1, low amplitude notched T waves typify LQT2, and a long isoelectric ST segment with late onset T waves or inappropriate sinus bradycardia are seen in LQT3.[2] Recognizing such ECG patterns allows for prediction of the genotype with a sensitivity of 83%

Figure 3: Alterations in T wave patterns associated with LQTS[18]

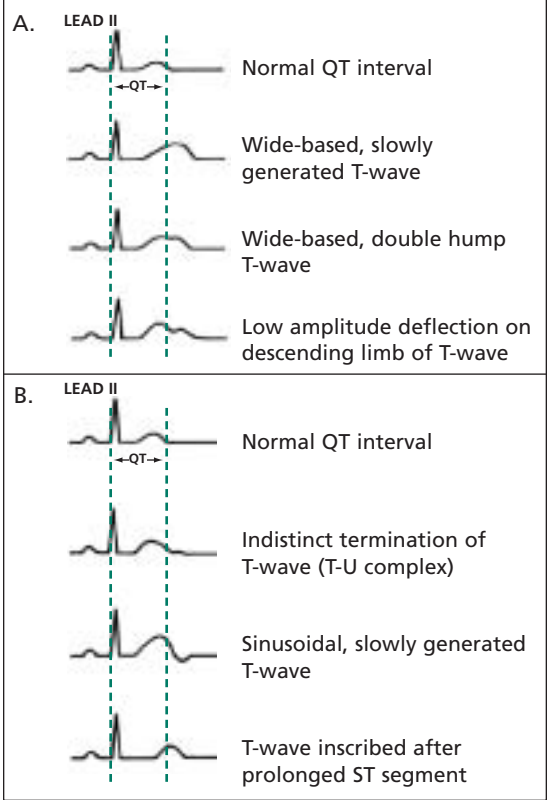
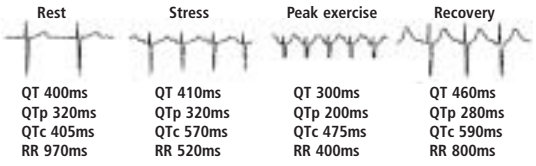


Figure 4: ECGs of a patient with long QT 1 (LQT1) undergoing exercise testing (V3 lead).[2] At rest, there is borderline QT prolongation. With emotional stress and exercise, there is marked rate-corrected QT interval (QTc) prolongation, reflecting impaired function of the slowly activating component of the delayed rectifier current (QT interval was underestimated because of the difficulty in extrapolating from peak to baseline). During recovery the QTc is still prolonged, but it eventually returned to baseline values. QTp = Duration from the Q wave to the peak of the T wave.



and a specificity of 70%-94%.[2] The QT interval can normalize with age, especially in men.[10]

The response of QT interval to change in heart rate is complex. During exercise or hyperadrenergic states, the QT interval in affected patients fails to shorten appropriately or may even prolong and this QT interval prolongation can persist to recovery (Figure 4). Patients with LQT3 mutations have greater QT interval shortening than other LQTS types or in controls, reflecting a normal potassium channel function. Other tests to elicit abnormal QT prolongations include epinephrine, dobutamine, or isoproterenol infusion.

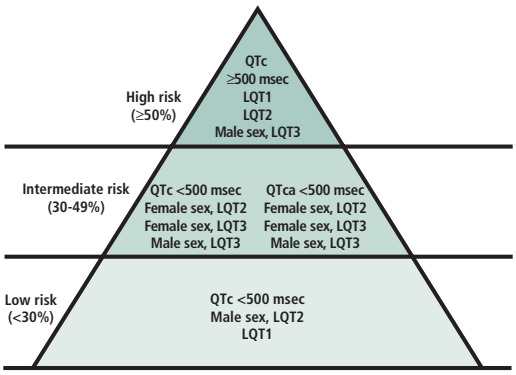
Symptoms of the LQTS

Symptoms of inherited LQTS may start in the first months of life or as late as middle age. Most commonly, however, signs and symptoms first appear during the preteen and teenage years. Approximately 50% of affected patients never develop any signs or symptoms.[12] The most common symptom is unexplained syncope, usually occurring during exercise, intense physical activity (eg, swimming or running), strong emotions (crying, stressful situations), or with startling noises (doorbell, phone ringing, alarm clock). Triggers for symptoms may vary, depending on the specific genetic defect. Exercise onset suggests an LQT1 genetic defect, whereas sound triggers or emotional upset onset tend to occur more often in people with LQT2. Symptoms may also occur at rest or during sleep in LQT3 (a relatively rare form of the syndrome). In about 5% of people with inherited LQTS, the first sign is sudden cardiac death. Not only is long QT syndrome often undiagnosed, it is frequently misdiagnosed as a seizure disorder.

Prognosis

In general, the risk of arrhythmia is directly proportional to the extent of QTc prolongation.[2,12] In untreated

Figure 5: Proposed scheme for risk stratification among patients with LQTS according to genotype and sex.[16] The risk groups were defined on the basis of the probability of a first cardiac event (syncope, cardiac arrest, or sudden cardiac death) before age of 40 years. A probability of 50% or higher defines the high-risk group, a risk of 30%-49% the intermediate-risk group, and a risk below 30% the low risk group.



symptomatic LQTS patients, the annual risk of syncope is 5% and the 10-year mortality is 50%.[2,13] In treated patients, mortality can be reduced to 3%-5% in 5 years.[14] In a selected LQTS registry, Zareba et al[15] demonstrated that the risk of cardiac events is higher among patients with mutations at the LQT1 or LQT2 locus than among LQT3 patients, but mortality was the same in all 3 groups because events were more likely to be fatal in LQT3 patients.

A more recent study[16] provided additional insights into the natural history and risk stratification of the disease by investigating a large unselected database. A risk stratification model was developed, as shown in Figure 5.

Treatment

For acquired LQTS, treatment is aimed at identifying and removing or correcting the underlying risk factors – including hypokalemia or hypomagnesemia – that are causing the LQTS. Since the most common cause is due to drug-induced QT prolongation, the offending agent needs to be identified and discontinued. It may be unclear which drug is the culprit, especially in ill patients in intensive care units receiving multiple drugs. The most important step is to consider acquired LQTS in any patient with polymorphic ventricular tachycardia, a prolonged QT interval and/or the typical initiating sequence shown in Figure 1. The simplest initial treatment is intravenous magnesium. Increasing the heart rate to >100 beats per minute (BPM) with isoproterenol infusion, atropine, or temporary pacing can also be very effective. It is very important for individuals with a history of LQTS to avoid medications that prolong the QT interval or deplete potassium or magnesium (eg, diuretics).

For inherited LQTS, the most common first-line drug therapy is a beta-blocker, which can reduce the risk of syncope and sudden death by 75%. Beta-blockers appear to be more effective in LQT1 than in LQT3. Therapy should provide complete beta-receptor blockade as defined by a target heart rate of <130 BPM at peak exercise.

There are limitations associated with long-term beta-blocker therapy including difficulties with long-term compliance, side effects, and the occasional failure to prevent symptoms despite adequate beta-blockade, especially in patients who have been resuscitated from sustained ventricular tachycardia or ventricular fibrillation. Experimental therapies for particular forms of LQTS are under investigation, including sodium channel blockers (eg, mexilitine for LQT3) or ion channel-specific therapy (eg, Nicorandil, a K-channel opener) for LQT2 or LQT3.

ICDs (implantable cardioverter defibrillators)

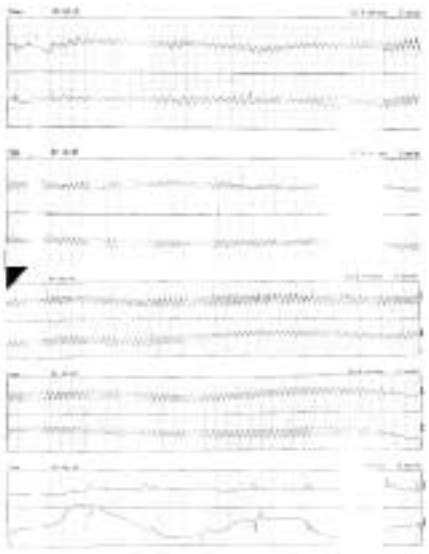
An ICD is indicated for all patients with documented ventricular fibrillation or aborted cardiac arrest. It is also indicated for patients who continue to have symptoms despite adequate beta-blockade. The role of ICDs as prophylaxis in patients with no prior history of syncope or documented ventricular tachycardia is undefined.

Left cervical sympathectomy can be utilized occasionally in patients with refractory symptoms despite other forms of therapy.

Conclusion

Only a limited number of patients with LQTS are expected to have an identifiable gene mutation, thus the

Figure 6: Holter monitor showing ventricular fibrillation in a 27-year-old patient with syncope



clinical usefulness of screening for mutations remains to be established. Patients with borderline or prolonged QT interval or patients with a normal QT interval, but a family history of sudden cardiac death from LQTS, should be carefully assessed. In-depth questions about personal and family history are very important in diagnosing LQTS. A family history of unexplained sudden cardiac death in a first-degree relative who was < 55 years of age, unexplained drowning of a young person, a history of syncope with exercise or after startle (often from loud sounds such as an alarm clock) are very helpful in diagnosing LQTS. Diagnostic criteria in Table 2 can be used and a referral to a cardiologist may be recommended if the probability of LQTS is intermediate or high. The risk of TdP is highly variable. In a patient with a prior history of acquired LQTS and TdP, or markedly prolonged QT interval (eg, >520 ms), any of the factors in Table 2 can cause TdP and need to be avoided if at all possible.

Follow-up of the Clinical Case

A Holter monitor was applied to the patient. She had an episode of syncope with full recovery. An ECG recorded at the time of syncope is illustrated in Figure 6. This patient received an ICD and a beta-blocker; she continues to have multiple appropriate ICD shock therapies for ventricular fibrillation.

Useful LQT Syndrome resources

- Cardiac Arrhythmia Research and Education (CARE) Foundation: www.longqt.org
- Cardiac Arrest Survivors Network: www.casn-network.org
- International registry for drug-induced Arrhythmia: www.qtdrugs.org

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