Long QT syndrome

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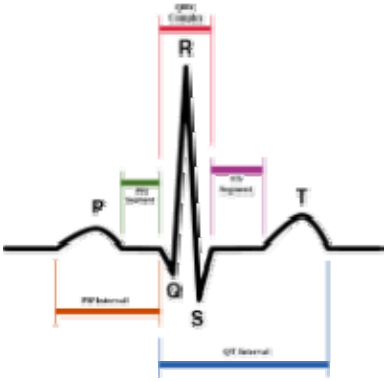
Long QT syndrome
Classification & external resources



Schematic representation of normal ECG trace *(sinus rhythm)*, with waves, segments, and intervals labeled.

ICD-10	I45.8
ICD-9	426.82
DiseasesDB	11104
eMedicine	med/1983
MeSH	D008133

The **long QT syndrome** (**LQTS**) is a heart disease in which there is an abnormally long delay between the electrical excitation (or depolarization) and relaxation (repolarization) of the ventricles of the heart. It is associated with syncope (fainting) and with sudden death due to ventricular arrhythmias. Arrhythmias in individuals with LQTS are often associated with exercise or excitement. The cause of sudden cardiac death in individuals with LQTS is ventricular fibrillation.

Individuals with LQTS have a prolongation of the QT interval on the ECG. The Q wave on the ECG corresponds to ventricular depolarization while the T wave corresponds to ventricular repolarization. The QT interval is measured from the Q point to the end of the T wave. While many individuals with LQTS have persistent prolongation of the QT interval, some individuals do not always show the QT prolongation; in these individuals, the QT interval may prolong with the administration of certain medications.

Contents

Genetics

The two most common types of LQTS are genetic and drug-induced. Genetic LQTS can arise from mutation to one of several genes. These mutations tend to prolong the duration of the ventricular action potential (APD), thus lengthening the QT interval. LQTS can be inherited in an autosomal dominant or an autosomal recessive fashion. The autosomal recessive forms of LQTS tend to have a more severe phenotype, with some variants having associated syndactyly (LQT8) or congenital neural deafness (LQT1). A number of specific genes loci have been identified that are associated with LQTS. Following is a list of the most common mutations:

Type	OMIM	Mutation	Notes
LQT1	192500	mutations to the alpha subunit of the slow delayed rectifier potassium channel (KvLQT1 or KCNQ1).	The current through the heteromeric channel (KvLQT1 + minK) is known as I_{Ks}. These mutations often cause LQT by reducing the amount of repolarizing current that is required to terminate the action potential, leading to an increase in the action potential duration (APD). These mutations tend to be the most common yet least severe.
LQT2	152427	mutations to the alpha subunit of the rapid delayed rectifier potassium channel (HERG + MiRP1).	Current through this channel is known as I_{Kr}. This phenotype is also probably caused by a reduction in repolarizing current.
LQT3	603830	mutations to the alpha subunit of the sodium channel (SCN5A).	Current through this channel is commonly referred to as I_{Na}. Depolarizing current through the channel late in the action potential is thought to prolong APD. The late current is due to failure of the channel to remain inactivated and hence enter a bursting mode in which significant current can enter when it should not. These mutations are more lethal but less common.
LQT4	600919	mutations in an anchor protein Ankyrin B which anchors the ion channels in the cell.	Very rare.
LQT5	176261	mutations in the beta subunit MinK (or KCNE1) which coassembles with KvLQT1.	-
LQT6	603796	mutations in the beta subunit MiRP1 (or KCNE2) which coassembles with HERG.	-
LQT7	170390	mutations in the potassium channel KCNJ2 (or $K_{ir}2.1$) which leads to Andersen-Tawil syndrome.	The current through this channel and KCNJ12 ($K_{ir}2.2$) is called I_{K1}.
LQT8	601005	mutations in the alpha subunit of the calcium channel Cav1.2 encoded by the gene CACNA1c.	Leads to Timothy's syndrome.
LQT9		mutations in Caveolin 3	
LQT10		mutations in SCN4B	

Drug induced LQT is usually a result of treatment by anti-arrhythmic drugs such as amiodarone or a number of other drugs that have been reported to cause this problem (e.g. cisapride). Some anti-psychotic drugs, such as Haloperidol and Ziprasidone, have a prolonged QT interval as a rare side effect. Genetic mutations may make one more prone to drug induced LQT.

LQT1

LQT1 is the most common type of long QT syndrome, making up about 40 to 55 percent of all cases. The LQT1 gene

is KCNQ1 which has been isolated to chromosome 11p15.5. KCNQ1 codes for the voltage-gated potassium channel KvLQT1 that is highly expressed in the heart. It is believed that the product of the KCNQ1 gene produces an alpha subunit that interacts with other proteins (particularly the minK beta subunit) to create the I_{Ks} ion channel, which is responsible for the delayed potassium rectifier current of the cardiac action potential.

Mutations to the KCNQ1 gene can be inherited in an autosomal dominant or an autosomal recessive pattern in the same family. In the autosomal recessive mutation of this gene, homozygous mutations in KVLQT1 leads to severe prolongation of the QT interval (due to near-complete loss of the I_{Ks} ion channel), and is associated with increased risk of ventricular arrhythmias and congenital deafness. This variant of LQT1 is known as the Jervell and Lange-Nielsen syndrome.

Most individuals with LQT1 show paradoxical prolongation of the QT interval with infusion of epinephrine. This can also unmark latent carriers of the LQT1 gene.

Many missense mutations of the LQT1 gene have been identified. These are often associated with a high risk percentage of symptomatic carriers and sudden death.

LQT2

The LQT2 type is the second most common gene location that is affected in long QT syndrome, making up about 35 to 45 percent of all cases. This form of long QT syndrome most likely involves mutations of the *human ether-a-go-go related gene* (HERG) on chromosome 7. The HERG gene (also known as KCNH2) is part of the rapid component of the potassium rectifying current (I_{Kr}). (The I_{Kr} current is mainly responsible for the termination of the cardiac action potential, and therefore the length of the QT interval.) The normally functioning HERG gene allows protection against early after depolarizations (EADs).

Most drugs that cause long QT syndrome do so by blocking the I_{Kr} current via the HERG gene. These include erythromycin, terfenadine, and ketoconazole. The HERG channel is very sensitive to unintended drug binding due to two aromatic amino acids, the tyrosine at position 652 and the phenylalanine at position 656. These amino acid residues are poised so drug binding to them will block the channel from conducting current. Other potassium channels do not have these residues in these positions and are therefore not as prone to blockage.

LQT3

The LQT3 type of long QT syndrome involves mutation of the gene that encodes the alpha subunit of the Na^+ ion channel. This gene is located on chromosome 3p21-24, and is known as SCN5A (also hH1 and $Na_V1.5$). The mutations involved in LQT3 slow the inactivation of the Na^+ channel, resulting in prolongation of the Na^+ influx during depolarization. Paradoxically, the mutant sodium channels inactivate more quickly, and may open repetitively during the action potential.

A large number of mutations have been characterized as leading to or predisposing LQT3. Calcium has been suggested as a regulator of SCN5A, and the effects of calcium on SCN5A may begin to explain the mechanism by which some these mutations cause LQT3. Furthermore mutations in SCN5A can cause Brugada syndrome, Cardiac Conduction disease and dilated cardiomyopathy. Rarely some affected individuals can have combinations of these diseases.

LQT5

is an autosomal dominant relatively uncommon form of LQTS. It involves mutations in the gene KCNE1 which encodes for the potassium channel beta subunit MinK. In its rare homozygous forms it can lead to Jervell and Lange-Nielsen syndrome

LQT6

is an autosomal dominant relatively uncommon form of LQTS. It involves mutations in the gene KCNE2 which encodes for the potassium channel beta subunit MiRP1, constituting part of the I_{Kr} repolarizing K^+ current.

LQT7

Andersen-Tawil syndrome is an autosomal dominant form of LQTS associated with skeletal deformities. It involves mutation in the gene KCNJ2 which encodes for the potassium channel protein Kir 2.1. The syndrome is characterized by Long QT syndrome with ventricular arrhythmias, periodic paralysis and skeletal developmental abnormalities as clinodactyly, low-set ears and micrognathia. The manifestations are highly variable.[1]

LQT8

Timothy's syndrome is due to mutations in the calcium channel Cav1.2 encoded by the gene CACNA1c. Since the Calcium channel Cav1.2 is abundant in many tissues, patients with Timothy's syndrome have many clinical manifestations including congenital heart disease, autism, syndactyly and immune deficiency.

LQT9

This newly discovered variant is caused by mutations in the membrane structural protein, caveolin-3. Caveolins form specific membrane domains called caveolae in which among others the $Na_V1.5$ voltage-gated sodium channel sits. Similar to LQT3, these particular mutations increase so-called 'late' sodium current which impairs cellular repolarization.

LQT10

This novel susceptibility gene for LQT is *SCN4B* encoding the protein $Na_V\beta4$, an auxiliary subunit to the pore-forming $Na_V1.5$ (gene: *SCN5A*) subunit of the voltage-gated sodium channel of the heart. The mutation leads to a positive shift in inactivation of the sodium current, thus increasing sodium current. Only one mutation in one patient has so far been found.

Associated syndromes

A number of syndromes are associated with LQTS.

Jervell and Lange-Nielsen syndrome

The Jervell and Lange-Nielsen syndrome (JLNS) is an autosomal recessive form of LQTS with associated congenital deafness. It is caused specifically by mutation of the KCNE1 and KCNQ1 genes.

In untreated individuals with JLNS, about 50 percent die by the age of 15 years due to ventricular arrhythmias.

Romano-Ward syndrome

Romano-Ward syndrome is an autosomal dominant form of LQTS that is *not* associated with deafness.

Mechanism of arrhythmia generation

All forms of the long QT syndrome involve an abnormal repolarization of the heart. The abnormal repolarization causes differences in the "refractoriness" of the myocytes. After-depolarizations (which occur more commonly in LQTS) can be propagated to neighboring cells due to the differences in the refractory periods, leading to re-entrant ventricular arrhythmias.

It is believed that the so-called early after-depolarizations (EADs) that are seen in LQTS are due to re-opening of L-type calcium channels during the plateau phase of the cardiac action potential. Since adrenergic stimulation can increase the activity of these channels, this is an explanation for why the risk of sudden death in individuals with LQTS is increased during increased adrenergic states (ie exercise, excitement) -- especially since repolarization is impared. Normally during adrenergic states, repolarizing currents will also be enhanced to shorten the action potential. In the absence of this shortening and the presence of increased L-type calcium current, EADs may arise.

The so-called delayed after-depolarizations (DADs) are thought to be due to an increased Ca^{2+} filling of the sarcoplasmic reticulum. This overload may cause spontaneous Ca^{2+} release during repolarization, causing the released Ca^{2+} to exit the cell through the $3Na^{+}/Ca^{2+}$-exchanger which results in a net depolarizing current.

Diagnosis

The diagnosis of LQTS is not easy since 2.5% of the healthy population have prolonged QT interval, and 10% of LQTS patients have a normal QT interval. A commonly used criterion to diagnose LQTS is the LQTS "diagnostic score" [2]. Its based on several criteria giving points to each. With 4 or more points the probability is high for LQTS, and with 1 or less point the probability is low. Two or 3 points indicates intermediate probability.

- QTc (Defined as QT interval / square root of RR interval)
  - >= 480 msec - 3 points
  - 460-470 msec - 2 points
  - 450 msec and male gender - 1 point
- Torsades de Pointes ventricular tachycardia - 2 points
- T wave alternans - 1 point
- Notched T wave in at least 3 leads - 1 point
- Low heart rate for age (children) - 0.5 points
- Syncope (one cannot receive points both for syncope and Torsades de pointes)
  - With stress - 2 points
  - Without stress - 1 point
- Congenital deafness - 0.5 points
- Family history (the same family member cannot be counted for LQTS and sudden death)
  - Other family members with definite LQTS - 1 point
  - Sudden death in immediate family (members before the age 30) - 0.5 points

Treatment options

There are two treatment options in individuals with LQTS: arrhythmia prevention, and arrhythmia termination.

Arrhythmia prevention

Arrhythmia suppression involves the use of medications or surgical procedures that attack the underlying cause of the arrhythmias associated with LQTS. Since the cause of arrhythmias in LQTS is after depolarizations, and these after depolarizations are increased in states of adrenergic stimulation, steps can be taken to blunt adrenergic stimulation in these individuals. These include:

- Administration of beta receptor blocking agents which decreases the risk of stress induced arrhythmias. Beta blockers are the first choice in treating Long QT syndrome.

In 2004 it has been shown that genotype and QT interval duration are independent predictors of recurrence of life-threatening events during beta-blockers therapy. Specifically the presence of QTc >500ms and LQT2 and LQT3 genotype are associated with the highest incidence of recurrence. In these patients primary prevention with ICD (Implantable Cardioverster Defibrilator) implantaion can be considered.[3]

- Potassium supplementation. If the potassium content in the blood rises, the action potential shortens and due to this reason it is believed that increasing potassium concentration could minimize the occurrence of arrhythmias. It should work best in LQT2 since the HERG channel is especially sensible to potassium concentration, but the use is experimental and not evidence based.
- Mexiletine. A sodium channel blocker. In LQT3 the problem is that the sodium channel does not close properly. Mexiletine closes these channels and is believed to be usable when other therapies fail. It should be especially effective in LQT3 but there is no evidence based documentation.
- Amputation of the cervical sympathetic chain (left stellectomy). This may be used as an add-on therapy to beta blockers but modern therapy mostly favors ICD implantation if beta blocker therapy fails.

Arrhythmia termination

Arrhythmia termination involves stopping a life-threatening arrhythmia once it has already occurred. The only effective form of arrhythmia termination in individuals with LQTS is placement of an implantable cardioverter-defibrillator (ICD). ICD are commonly used in patients with syncopes despite beta blocker therapy, and in patients who have experienced a cardiac arrest.

With better knowledge of the genetics underlying the long QT syndrome, more precise treatments will be readily available.[4]

Risk stratification

The risk for untreated LQTS patients having events (syncopes or cardiac arrest) can be predicted from their genotype (LQT1-8), gender and corrected QT interval.[5]

- High risk (>50%)

QTc>500 msec LQT1 & LQT2 & LQT3(males)

- Intermediate risk (30-50%)

QTc>500 msec LQT3(females)

QTc<500 msec LQT2(females)& LQT3

- Low risk (<30%)

QTc<500 msec LQT1 & LQT2 (males) \

References

1. ^ Tristani-Firouzi M, Jensen JL, Donaldson MR, Sansone V, Meola G, Hahn A, Bendahhou S, Kwiecinski H, Fidzianska A, Plaster N, Fu YH, Ptacek LJ, Tawil R. Functional and clinical characterization of KCNJ2 mutations associated with LQT7 (Andersen syndrome). Journal of Clinical Investigation. 2002 Aug;110(3):381-8. PMID 12163457.
2. ^ Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome. An update. Circulation. 1993 Aug;88(2):782-4. PMID 8339437.
3. ^ Priori SG, Napolitano C, Schwartz PJ, Grillo M, Bloise R, Ronchetti E, Moncalvo C, Tulipani C, Veia A, Bottelli G, Nastoli J. Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. JAMA. 2004 Sep 15;292(11):1341-4. PMID: 15367556
4. ^ Compton SJ, Lux RL, Ramsey MR, Strelich KR, Sanguinetti MC, Green LS, Keating MT, Mason JW. Genetically defined therapy of inherited long-QT syndrome. Correction of abnormal repolarization by potassium. Circulation. 1996 Sep 1;94(5):1018-22. PMID 8790040

5. ^ Risk Stratification in the Long-QT Syndrome: N Engl J Med 2003; 349:908-909, Aug 28, 2003. PMID 12944579.

See also

- Cardiac action potential
- Short QT syndrome

External links

- C.A.R.E. Foundation - Cardiac Arrhythmia Research and Education Foundation, Inc.
- Arizona CERT - QT Drug Lists
- The Long QT Syndrome Support Center - LQTS Info for Patients and Physicians
- Drugs that Prolong the Qt Interval and/or Induce Torsades de Pointes Ventricular Arrhythmia
- Sudden Arrhythmia Death Syndromes (SADS) Foundation
- QTsyndrome.ch. Here LQTS patients can ask questions and get answers
- Mutation database of inherited arrhythmias including Long QT syndrome