Long QT syndrome

# Definition

Long QT syndrome (LQTS) can be defined asan inheritedcondition associated with a prolongation of theQT interval on the ECG characterized by syncope,seizures, and sudden death secondary to ventricular arrhythmia,specifically torsade de pointes1. It may be congenital or acquired.

# Prevalence of congenital LQTS

A recent study of 43 080 white infants 15 to 25 days old identified 17 who were affected by LQTS, demonstrating a prevalence of at least 1:2534 apparently healthy live births (95% confidence interval, 1:1583 to 1:4350)2. This is now considered to be the most authoritative estimate of the prevalence of this condition.

# Diagnosis

## The ECG

The ECG is the key to diagnosis. Generally, at rest, in men at QTc of > 450ms or in women > 470ms is considered abnormal (Table 1). There are often associated T-wave abnormlities, which may give a clue as to the genotype. However, interpreting the QT interval is by no means straight-forward and there remains controversy3, 4. There is considerable variability in QTc duration during serial follow-up5. Furthermore, in 12-30% of patients with LQTS the resting ECG may have a normal QTc interval at rest6, 7. Conversely a proportion of the normal population may have a modestly prolonged QT interval8.

### Table 1:. Suggested Bazett Corrected QTc values for diagnosing QT prolongation9

|  |  |  |  |
| --- | --- | --- | --- |
| **QT Interval** | **1-15 Years** | **Adult Male** | **Adult Female** |
| Normal (ms) | < 440  | < 430 | < 450 |
| Borderline (ms) | 440–460 | 430–450 | 450–470 |
| Prolonged (ms) | > 460 | > 450 | > 470 |

Reversible causes and other conditions must be excluded. In brief, drugs are probably the most common cause. A list of drugs which can prolong the QT interval can be found here: <http://www.azcert.org/medical-pros/drug-lists/browse-drug-list.cfm>. Electrolyte disturbances must also be considered – particularly hypokalaemia, hypomagnesaemia and hypocalcaemia. Intracranial events may also cause QT prolongation, particularly intracranial haemorrhage. Following resuscitation from cardiac arrest the QT interval may remain prolonged for several months (Moss A J, personal communication). Elite athletes may have modest prolongations in their QT interval without having LQTS10. Patients with dilated or hypertrophic cardiomyopathy may also have a prolonged QT interval11, 12. In catecholaminergic polymorphic ventricular tachycardia (CPVT) the QT interval may be modestly prolonged13 and, for interest, it should be remembered that LQT7 (Andersen-Tawil syndrome) can present with bidirectional VT14, which is typically thought to be characteristic of CPVT. Other conditions to be considered include anorexia nervosa, liver disease and diabetes mellitus 15, 16. The QTc is prolonged in patients withcardiac amyloid, but this does not seem to correlate withlife-threatening arrhythmias17.

## The Schwartz scoring system

The Schwartz scoring system18 is widely used but does not take into account additional genetic information. It is reproduced below in table 2.

### Table 2 – Schwartz scoring system for diagnosis of LQTS

|  |  |
| --- | --- |
|  | **Points** |
| **ECG Findings1** |  |
| A | QTc2 |  |
|  |  ≥ 480ms | 3 |
|  |  460-470ms | 2 |
|  |  450-460ms (in males) | 1 |
| B | Torsades de pointes3 | 2 |
| C | T-Wave alternans | 1 |
| D | Notched T wave in 3 leads | 1 |
| E | Low heart rate for age4 | 0.5 |
| Clinical History |  |
| A | Syncope3 |  |
|  |  With stress | 2 |
|  |  Without stress | 1 |
| B | Congenital deafness |  |
| Family History5 |  |
| A | Family members with definite LQTS | 1 |
| B | Unexplained sudden cardiac death below age 30 among immediate family members | 0.5 |
|  |  |  |
| **Notes** |
| 1 | In the absence of medications or disorders known to affect these ECG features |
| 2 | QTc calculated by Bazett’s formula, where QTc=QT/√RR |
| 3 | Mutually exclusive |
| 4 | Resting heart rate below the 2nd percentile for age19 |
| 5 | The same family member cannot be counted in A and B |
|  |  |
| **Scoring** |
| Definite | ≥ 4 |
| Intermediate probability | 2-3 |
| Low probability | ≤1 |
|  |  |  |

## History

The history can point to a diagnosis of LQTS. In particular patients should be asked if they have:

* fainted or become dizzy with exercise, fear or strong emotions
* developed palpitations with exercise, fear or strong emotions
* been treated for a seizure disorder8

Syncope with exercise, particularly swimming tends to point towards a diagnosis of LQT1. Symptoms following emotional stimulation, particularly fear, or strong auditory stimuli seem more common in patients with LQT2. LQT3 syndrome tends to be associated with problems that occur during sleep.

Of note LQT1 tends to present before the age of 9, whereas LQT2 and 3 tend to present in teenagers, although cases can remain undiagnosed until adulthood.

A full drug history should be taken, including a history of over-the-counter medications and herbal remedies20.

A history of deafness is important. The Jervell-Lange-Nielsen syndrome – the combination of a long QT interval and congenital deafness was the first of the Long QT syndromes to be described in 195721.

Finally a comprehensive family history should be taken. A family history of LQTS or unexplained sudden cardiac death raises the likelihood of the index case having LQTS.

## Examination

Typically findings on examination will not reveal the diagnosis of LQTS. Some patients may have excessive bradycardia or deafness. Scoliosis and short stature may be seen in LQTS type 722 (Andsersen-Tawil syndrome). LQTS type 823 (Timothy syndrome) is characterised by co-existent congenital heart disease, cognitive dysfucntion, musculoskeletal problems and immune dysfunction. Examination may suggest an alternative diagnosis – for example a murmur may be heard from underlying hypertrophic cardiomyopathy.

## Routine investigations

### Echocardiography

Echocardiography should be normal in patients with LQTS. It would seem sensible, however, when investigating patients for LQTS to perform echocardiography routinely given the nature of the conditions outlines above which can incidentally prolong the QT interval.

### Holter monitoring

In patients where the diagnosis of LQTS is in doubt holter monitoring may reveal the diagnosis as the QT interval and QTc are variable over time.

### Exercise testing

In patients with borderline QT intervals, the dynamic behaviour of the QT interval during exercise testing may suggest the diagnosis. Exercise testing may also suggest an alternate diagnosis, particularly CPVT24.

## Other investigations

EP testing has not proved useful in risk stratification in patients with LQTS (See ACC/AHA/ESC 2006 guidelines, section 5.3.3.125).

## Genetic testing

LQTS is inherited in an autosomal dominant fashion.

Genetic testing is of value in LQTS, particularly as the QT interval may appear normal. In patients with LQTS genetic testing may be abnormal in up to ¾ of patients. It can be used to confirm the diagnosis of LQTS. It may also suggest appropriate therapy and it is beginning to help with risk stratification in quite a sophisticated way. It may facilitate the screening of relatives. If genetic testing for LQTS is negative it may be reasonable to screen for RyR2 mutations which are found in CPVT. Genetic testing for LQTS is recommended as part of a genetic autopsy.

It is important to remember that clinical screening alone cannot identify relatives of patients with LQTS who carry identical genetic mutations. Part of this may be due to erroneous computer-generated ECG diagnostic interpretation.

The genetics of LQTS are complex, and becoming increasingly so, and are summarised in table 3.LQT1, 2 and 3 comprise the majority of clinical cases.Importantly around 10% of patients have more than one mutation. It has been suggested that because double heterozygosity appears to be more common than expected, molecular diagnosis should be performed on all LQTS-related genes, notwithstanding the identification of a single mutation.

### Table 3. The genetics of LQTS

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of LQTS**  | **Chromosomal** Locus | **Mutated** Gene | **Ion Current Affected**  | **Prevalence** |
| **LQT1 (Romano-Ward syndrome)** | 11p15.5  | KCNQ1 | Potassium (IKs)  | 42% |
| **LQT2**  | 7q35-36  | KCNH2  | Potassium (IKr)  | 45% |
| **LQT3**  | 3p21-24  | SCN5A  | Sodium (INa)  | 8% |
| **LQT4**  | 4q25-27  | ANK2 | Sodium, potassium and calcium  | Rare |
| **LQT5 (Jervell and Lange-Nielsen syndrome)** | 21q22.1-22.2  | KCNE1 | Potassium (IKs)  | 3% |
| **LQT6**  | 21q22.1-22.2  | KNCE2  | Potassium (IKr)  | 2% |
| **LQT7 (Anderson syndrome)**  | 17q23.1-q24.2  | KCNJ2  | Potassium (IK1)  | Rare |
| **LQT8 (Timothy syndrome)**  | 12q13.3  | CACNA1C  | Calcium | Rare |
| **LQT9**  | 3p25.3  | CAV3  | Sodium (INa)  | 0.66% |
| **LQT10**  | 11q23.3  | SCN4B  | Sodium (INa)  | Single family |
| **LQT11**  | 7q21-q22  | AKAP9  | Potassium (IKs)  | Single family |
| **LQT12**  |  | SNTA1 | Sodium (INa)  | Single family |

Risk prediction is complex. Although events in LQT1 are more common than in LQT2 and LQT3, events which do occur in these latter two conditions carry a higher risk of death. For patients with LQT1 and LQT2 syndrome the genetic locus and the QTc are independent predictors of risk. For patients with LQT3 the QTc is not an independent predictor, but male patients were noted to be at higher risk, even when their QTc was < 500ms26. Patients with more than one mutation tend to have a longer QTc and a significantly higher risk of death.

The current UK stance recommends genetic testing for confirmed clinical cases of LQTS only27. A confirmed clinical case would correspond with a Schwartz score of ≥ 4. Genetic testing of 1st degree relatives of an index case in whom the mutation has been identified is also recommended. Genetic testing for borderline cases to confirm or refute the diagnosis is not recommended routinely. The current approach is to target the most commonly involved genes, often in a sequential manner, although these guidelines will almost certainly change in the future as new sequencing techniques become available and costs reduce.

# Management

The fact that this is a disease which has a genetic basis should be discussed with the patient and the potential need to screen relatives for the same condition should be broached. A more complete discussion of the implications is probably not practical in the cardiology out-patient setting and referral to a clinical genetics service is recommended. Genetic testing for the individual and relatives may be appropriate and a decision should be made by the cardiologist, geneticist and affected (or potentially affected) individual. A combination of phenotype and genotype can inform management.

It is reasonable to give lifestyle advice. In particular for LQT1 strenuous exercise should be avoided, particularly swimming, although avoidance of strenuous exercise is recommended for all forms of LQTS25. It may be appropriate to teach behavioural techniques to deal with stressful situations and avoid alarm clocks and phones by the bedside in patients with LQT2. All patients with LQTS should avoide drugs which prolong the QT interval or drugs which may result in electrolyte disturbance.

Beta-blockers are the mainstay of therapy in patients with LQTS and have been recommended for many years28. They should be given to patients with a genetic diagnosis of LQTS even if their QTc is normal. They are variably effective depending upon the type of LQTS29-31, but are particularly effective in Type 1 LQTS32.

Beta-blockers tend to be ineffective in LQT3. This is unsurprising given that arrhythmias tend to occur after exercise in LQT1, whereas they tend to occur at rest in LQT3. LQT3 is characterised by a gain of function of the sodium channel SCN5A; mexiletene, a sodium channel blocker, appears to be effective in LQT333.

In the USA over-the-counter sales of AEDs (Automatic external defibrillators) are approved for home use in patients with high risk inherited arrhythmias such as LQTS25.

The use of an ICD to treat patients with a LQTS who have survived cardiac arrest is a class I indication according to AHA/ACC/ESC and of course, NICE guidelines25, 34. The ESC/AHA guidelines include a long and detailed section on the management of LQTS, part of which is reproduced here; The NICE guidelines do not.

An ICD may be indicated for some patients with LQTS for primary prevention. The indications are not clearly defined and the decision must be individualised and will depend in part on the clinical presentation, the genotype and the fears and beliefs of the patient. Family history does not necessarily have any bearing on risk29, 35. A QTc ≥ 500ms and syncope or a history of aborted sudden cardiac death appear to be the best predictors of future events33. The precise genetic mutation may be a predictor of risk and a number of studies have identified higher risk mutations36-38. We recommend that cases of LQTS where an ICD may be contemplated for primary prevention should be discussed at a multi-disciplinary meeting, such as quarterly meeting held in our network.

The following section on ganglionectomy is taken directly from the ACC/AHA/ESC guidelines25. Left cervicothoracic sympathetic ganglionectomy wasintroduced in 1971 for the treatment of adrenergicallytriggered life-threatening ventricular arrhythmias associatedwith the LQTS39. This procedure, performed througha limited supraclavicular approach, involves resection of thelower half of the left stellate ganglion and removal of at leastthe second and third thoracic sympathetic ganglia on theleft side40. This surgical therapy is associated withreduction in the frequency of arrhythmogenic syncope inthis syndrome and may be useful as adjunctive therapy inhigh-risk LQTS patients who have recurrent syncopeand/or aborted cardiac arrest despite combined ICD andbeta-blocker therapy or in LQTS patients who cannottolerate beta blockers41.

A summary of ESC/AHA recommendations for Long QT Syndrome Recommendationsis reproduced from the guidelines below:

Class I

1. Lifestyle modification is recommended for patients with an LQTS diagnosis (clinical and/or molecular). *(Level of Evidence: B)*
2. Beta blockers are recommended for patients with an LQTS clinical diagnosis (i.e., in the presence of prolonged QT interval). *(Level of Evidence: B)*
3. Implantation of an ICD along with use of beta blockers is recommended for LQTS patients with previous cardiac arrest and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: A)*

Class IIa

1. Beta blockers can be effective to reduce SCD in patients with a molecular LQTS analysis and normal QT interval. *(Level of Evidence: B)*
2. Implantation of an ICD with continued use of beta blockers can be effective to reduce SCD in LQTS patients experiencing syncope and/or VT while receiving beta blockers and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: B)*

Class IIb

1. Left cardiac sympathetic neural denervation may be considered for LQTS patients with syncope, torsades de pointes, or cardiac arrest while receiving beta blockers. *(Level of Evidence: B)*
2. Implantation of an ICD with the use of beta blockers may be considered for prophylaxis of SCD for patients in categories possibly associated with higher risk of cardiac arrest such as LQT2 and LQT3 and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: B)*

# Summary

LQTS is a rare disorder which can be difficult to diagnose, as the QTc can be normal. Furthermore, risk stratification can be challenging. A genetic mutation can be identified in up to ¾ of patients and assists with the screening of relative and also potentially with risk stratification and is therefore recommended.

Also see: <http://bestpractice.bmj.com/best-practice/monograph/829/diagnosis/step-by-step.html>

# Situation 1: QTc interval noted to be prolonged



# Situation 2: 1st degree relative of patient (alive or dead) is diagnosed with LQTS



# Sample ECGS

(<http://bestpractice.bmj.com/best-practice/images/bp/829-4-iline_default.gif>)

## LQT1



LQT1 is characterised by prolonged QT intervals associated with a broad-based T wave42

## LQT2



LQT2 is characterised by low-amplitude and notched T waves42

## LQT3



LQT3 is characterised by long ST segments with a late-appearing T wave resulting in a long QT interval42

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