The Cardiac Society of Australia and New Zealand

Endorsed by:

Heart Foundation™

Guidelines for the diagnosis and management of Familial Long QT Syndrome

These guidelines were ratified at the CSANZ Board meeting held on Wednesday, 12th August, 2009.

1. Clinical Characteristics

1.1 Definition and prevalence

Long QT syndrome (LQTS) is a familial condition causing syncope and sudden death through rapid ventricular tachycardia (torsade de pointes), which can deteriorate to ventricular fibrillation, in otherwise fit and healthy young people. Prevalence is at least 1 in 5000 and may be up to 1 in 1000. Clinical diagnosis is made from a combination of suspicious history, family history and the twelve lead ECG, which typically reveals a heart-rate corrected QT interval (QT//R-R interval=QTc) of greater than 0.46 in women and 0.45 in men. Exercise testing and ECG evaluation of first degree relatives and provocative testing with exercise or drug challenge may be helpful in making the diagnosis.

1.2 Clinical presentation

LQTS most commonly presents with syncope or sudden death during or following exercise or stress in a young person. QT prolongation can present on an incidental ECG. Misdiagnosis of LQTS as epilepsy, particularly "familial epilepsy" is common. Seizures following exertion or arousal, and even during sleep, must raise the suspicion of LQTS.

Mutations within twelve genes are known to cause LQTS. Studies of the three commonest genotypes (Types 1, 2 and 3) have shown that syncope or sudden death tend to occur under specific circumstances in a gene-specific manner. For example, in LQT1 events are linked to exercise, especially swimming, LQT2 to loud noise and emotion, especially at night, and LQT3 to death during sleep. See Table 1.

Table 1. Molecular Genetics of Long QT Syndrome (LQTS)*

LQTS	Chromosomal Locus	Mutant Gene (Alternate Name)	Ion Currents Affected during repolarisation	Event triggers (%) Exercise	Emotion/noise	Rest
LQT1	11p15.5	*KCNQ1 (KVLQT1)*	K^+ (I_{Ks})	62	26	3
LQT2	7q35-36	*HERG*	K^+ (I_{Kr})	13	43	29
LQT3	3p21-24	*SCN5A*	Na^+ (I_{NA})	13	19	39
LQT4	4q25-27	Ankyrin B	Na^+ (I_{NA})			
LQT5	21q22.1-22.2	*KCNE1* (minK)	K^+ (I_{Ks})			
LQT6	21q22.1-22.2	*KCNE2* (MiRP1)	K^+ (I_{Kr})			
LQT7 †	17q23	*KCNJ2*	K^+ ($K_{ir2.1}$)			
LQT8 ^	12(12p13.3)	*CACNA1C*	Ca^{++}(I_{Ca-L})			
LQT9	3(3p25)	*CAV3*	Na^+ (I_{NA})			
LQT10	11(11q23.3)	*SCN4B*	Na^+ (I_{NA})			
LQT11	7	*AKAP9*	K^+ (I_{Ks})			
LQT12	20	*SNTA1*	Na^+ (I_{NA})			

*A single mutation (heterozygous state) in any one of the *LQT1 through LQT12* genes results in an autosomal dominant form of LQTS (Romano-Ward syndrome).
The presence of 2 mutations (homozygous state) in either the *LQT1* or *LQT5* gene results in a severe autosomal recessive form of LQTS with associated sensorineural deafness (Jervell and Lange-Nielsen syndrome).
†Mutations in *LQT7* are responsible for Anderson syndrome, a rare neurological disorder characterized by periodic paralysis, skeletal developmental abnormalities, and QT prolongation.
^Mutations in *CACNA1C* cause Timothy syndrome where severe long QT syndrome is associated with syndactyly, small teeth, autism and cardiac defects (such as PDA)

1.3 Clinical diagnosis

The diagnosis is usually made on clinical grounds- note the importance of clinical and family history as well as ECG findings (table 2). As well as QTc prolongation, the T-wave morphology is frequently abnormal and tends to vary between genotype; LQT1, broad based T-wave, LQT2 low voltage bifid T-wave, LQT3, high voltage late onset T-wave. QT prolongation due to drugs or biochemical imbalance (low potassium, calcium or magnesium), hypothermia and myocardial disease must be excluded.

QT intervals are best measured in lead II and V_5 since these are the most repeatable and correlate best to genotype status (Monnig 2006). Avoid leads V2 to V4 especially in children where over-interpretation of T-U complexes is common.

Features suggesting arrhythmic syncope, rather than neurocardiogenic syncope, include unheralded collapse associated with exercise, sudden emotional stress or loud noise, and physical injuries which indicate failure to make protective movements when falling- particularly facial injury. Syncope associated with swimming is due to LQTS (or Catecholaminergic Polymorphic VT) until proven otherwise. The implantable digital loop recorder can be valuable to differentiate benign syncope from VT. Syncope secondary to pain or nausea is more commonly neurally mediated.

Table 2. Clinical diagnostic criteria for LQTS*

Electrocardiogram Findings†	Points
Corrected QT interval, seconds	
≥0.48	3
0.46-0.47	2
0.45 (in males)	1
Torsades de pointes‡	2
T-wave alternans	1
Notched T wave in 3 leads	1
Low heart rate for ages§	0.5
Clinical history	
Syncope‡	
With stress	2
Without stress	1
Congenital deafness	0.5
Family history▒	
Family members with definite LQTS	1
Unexplained sudden cardiac death at under 30 years among immediate family member(s)	0.5

* Reprinted from Schwartz et al. *Circulation 1993,88:782-4*. Scoring: ≤1 point, low probability of LQTS; 2 to 3 points, intermediate probability of LQTS; and ≥4 points, high probability of LQTS.
† Findings in the absence of medications or disorders known to affect these electrocardiogram findings. The corrected QT interval (QTc) is calculated by the Bazett formula: $QTc = QT/\sqrt{RR}$, where R-R is the time interval between 2 consecutive QRS complexes on electrocardiogram.
‡ Torsades de pointes and syncope are mutually exclusive.
§ Resting heart rate below the second percentile for age.
▒ The same family member cannot be counted in both categories

Family history: A detailed family history looks for a history of syncope or sudden unexplained death in a close relative. Directed questioning is essential, with a family tree being drawn. Consider unexpected drowning in a strong swimmer, or road traffic accidents on a straight road. Document age and mode of death, or syncope in all close relatives. Familial epilepsy and sudden infant death are suspicious. Sudden death with negative post-mortem should trigger a family investigation for LQTS.

Family screening: ECGs should be obtained on all first-degree relatives. One third of asymptomatic gene mutation carriers have QTc values within the normal range. QTc values of ≥0.44 sec are treated as suspicious. Values below 0.41 sec are uncommon in gene carriers. The length of the QT interval is linked to the risk of syncope and sudden death, but all gene carriers are at an increased risk, and each of their children will have a 50% rise of carrying the mutation.

Certainty for many family members often requires genetic testing. Holter testing is limited for making the diagnosis unless torsade de pointes or T-wave alternans is documented. Exercise testing can be very helpful. After exercise, QT intervals of LQT mutation carriers and non-carriers tend to separate more than at rest. (An absolute QT interval of over 0.37sec at a heart rate of 100 post exercise is highly suggestive of LQTS types 1 or 2; a value below 0.34 sec makes it unlikely. (Swan 1999)

2. Molecular Genetics

2.1 Familial LQTS disease genes

LQTS is most commonly inherited in an autosomal dominant manner. Thus, each child of an affected parent has a 50% chance of inheriting a disease-causing gene mutation. Twelve genetic forms of LQTS are known where a dysfunctional cardiac cell channel results in prolongation of the cardiac action potential, and thus the QT interval (table 1). About one third of families with LQTS do not yet have a recognised genetic locus. The commonest genotypes are types 1 and 2; about 8% are type 3.

2.2 Genetic screening

Commercially available LQT genetic testing is now available from several clinically accredited laboratories around the world, including New Zealand and Australia. Most will sequence the genes linked to LQT types 1,2,3,5,6 and 7 only; the others being rare. It is now recognised that sequencing can miss large gene rearrangements, so gene dosage evaluation should now follow uninformative gene sequencing analysis, especially if the family history is highly malignant (Eddy 2008).

Defining the genotype does influence management (see below), but the main value of genetic testing lies in family screening. Following the identification of a proband who unequivocally has LQTS, molecular diagnosis is then sought through screening the known genes. Hundreds of mutations within the genes have been identified, and these genes carry many polymorphisms (harmless genetic variations), so that this first molecular diagnosis is time consuming. However, once the mutation is found, screening for this point mutation in the family is relatively quick.

Careful counselling prior to testing is essential, and confidentiality of results needs to be assured. Some people will not want their own GP or their family to know their result. Negative aspects of a positive genetic diagnosis include potential insurance and employment and psychological problems. Patients are warned that genetic variants may be found which are of uncertain significance.

3. Management

3.1 Affected individuals

Once diagnosed, patients with LQTS should have cardiological follow-up long term. Registration with an inherited disease registry may facilitate family screening, advice regarding novel therapies, and participation in research programmes.

Removal of triggers: All gene carriers must avoid medications which prolong the QT interval, cause torsade de pointes or lower serum potassium levels. A constantly updated list is available at www.qtdrugs.org.

With all forms of LQTS some degree of limitation in sporting activity is required. The limitation needs to be more severe with LQT1, or those who have already experienced events during exercise, than LQT2 and 3. They should not become professional athletes, and all highly competitive sports are to be discouraged. With LQT 1, and subjects with a history of exercise induced syncope, swimming and diving are contraindicated. With LQT 2, or those with a history of auditory evoked events, remove loud alarm clocks and turn down the volume on the phone at night.

Assessment of risk: Data from the international long QT registry has shown that risk of sudden death varies between genotype, gender, age and length of QT interval and, especially important, previous symptomatology (Goldenberg 2008a, Hobbs 2006, Sauer 2007, Goldenberg 2008b). Family history of sudden death does not *per se* increase risk. In girls under 12 years, the only factor linked to risk is prior syncope. In adults, the most important risk factors are a history of more than 10 syncopal events before age 18 years, and a QTc >550ms.

Those at highest risk are those with a QTc over 550ms (20% of 18 year olds with a QTc>550ms will have a cardiac arrest by aged 40- Sauer 2007). Among these higher still are males from 5-20 years with LQT1, female adults with LQT2, and young adult males with LQT3. A history of prior syncope increases the hazard ratio by 27 fold in girls, ten fold in adults, and six fold in boys.

Those at lowest risk are asymptomatic males over 30 years of age with a QTc below 500ms and with either LQT1 or LQT2.

Beta Blockade: Beta blockade should be initiated in those who have had symptoms, and those with a definite long QT interval, particularly in young people, including male infants with LQT1. Beta blockers reduce the risk of sudden death by 50-75% in LQT1 and approximately 50% in LQT2, though they are not yet of proven value in older patients (>40 years; Sauer 2007). However the risk is not reduced to zero. Boys on beta blockers who had syncope before 6years of age still had a 7% chance of sudden cardiac death by age 12. *Post-partum mothers are at especially high risk and must also take beta blockers for at least 9 months* (Seth 2007), whereas risk during pregnancy is normal or low. Long acting agents taken once a day are preferred to aid compliance. Once started, they should not be stopped; there is a period of high risk after stopping beta-blockers due to up-regulation of beta-receptors on treatment.

LQT3 patients are at higher risk at slower heart rates, and the QT interval shortens at faster heart rates. This raises concerns, not yet supported by evidence, regarding the use of beta-blockers. The prevention of noradrenaline release remains important, but it may be more safely achieved with selective left cardiac sympathetic denervation, which does not reduce heart rate. LQT3 patients may benefit from pacemakers, which would also allow the safe use of beta-blockers, though since there is a high mortality rate even at the first episode, especially in males with a long QT interval, early consideration of AICD is reasonable.

No gene-specific therapies have proven effect in reducing risk of death, nor are they yet known to be safe. QT interval can be shortened, and may be of value in VT storms, with potassium pump enhancing agents, such as nicorandil, in LQT type 1, spironolactone combined with oral potassium in LQT type 2, and sodium channel blockers, such as flecainide, in LQT type 3.

Cardioverter-defibrillators (AICD): These are indicated for:
1. Resuscitated cardiac arrest;
2. Persistent syncope whilst on beta blockers;
3. When beta blockers are contra-indicated.

A relative indication is the presence of a very long QT interval (QTc>0.55sec) even without symptomatology, particularly in males with LQT 3, and females with Long QT2 (in whom risk does not decrease during adult life). Unless inserted for contraindication to beta-blockers it is important that beta-blockers are continued because of the risk that a defibrillation shock may cause an adrenergic surge and precipitate a further event or electrical storm.

Left cervical sympathectomy: Selective left cervical sympathectomy, which can now be done thoracoscopically, may be considered for:
1. Those with severe disease and in whom beta blockers are contra-indicated or not adhered to, or an AICD cannot be placed or is not wanted;
2. Controlling VT storms in those with an AICD;
3. LQT3 or a personal or family history of events during rest or sleep.

3.2 Asymptomatic family members

If LQTS cannot be excluded, the individual should avoid medications contra-indicated in LQTS. Those with an unequivocally long QT interval need to be treated much as someone who has already presented with syncope. Beta blockers should be proposed and sensible limitations placed on sporting activities and particularly swimming.

The role of beta blockers in those without symptoms, a normal QT interval and yet a positive genetic diagnosis is controversial. Asymptomatic older males (>30) with LQT1 or LQT2 probably need no treatment. Those with a family history of adrenergic induced cardiac events, or known to have LQT1 between 5 and 15 years, are most likely to benefit.

3.3 Counselling

The main aim of the cardiologist is to prevent sudden death though medication and life-style changes. A secondary aim is to assist the family in their adjustments that have to be made. Time and skilled psychological and genetic counselling is required. This is often more than the busy cardiologist can provide and suitable professional assistance should be offered when appropriate. Some of those at highest risk are adolescents and teenagers. Beta blockers and the limitations on activities are both hard pills to swallow, and whilst encouraging compliance, it is important not to alienate the patient. They will need to feel some retention of control in their lives.

4. Further Information

For more information about this document please contact Dr Jon Skinner at Greenlane Paediatric and Congenital Cardiac Services, Starship Hospital, Park Road, Private Bag 92024, Auckland New Zealand.

Key References

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Useful Websites

www.cidg.org (Cardiac Inherited Disease Group New Zealand)
www.sads.org (International site of the Sudden Arrhythmic Death Society)
www.sads.org.au (Australian site)