Update on the Diagnosis and Management of Familial Long QT Syndrome

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Clinical Characteristics

Summary Overview

- Long QT syndrome (LQTS) is a familial condition causing syncope and sudden death through polymorphic ventricular tachycardia (torsades de pointes), which can deteriorate to ventricular fibrillation, in otherwise fit and healthy young people.
- Prevalence is approximately 1 in 2,500 \cite{1}.
- Clinical diagnosis is made from a combination of suspicious clinical history (sudden unheralded syncope or cardiac arrest typically associated with exercise, stress, startle or during sleep) and family history, and the 12 lead ECG.
- ECG typically reveals a heart-rate corrected QT interval (QT/\sqrt{R-R} interval = QTc) repeatedly greater than 470ms in women and 450ms in men, in the absence of other known factors prolonging the QT interval.
- High risk individuals are identified by QTc $\geq$ 500ms and/or syncope in the previous two years. Boys and post pubertal females (especially in the nine post-partum months) are high risk.
- Risk reduction is achieved through lifestyle modification, avoidance of QT prolonging drugs, beta blockade and less commonly with left cardiac sympathetic denervation or ICD insertion.

Changes from Previous 2011 Document

An expanded section is included on QTc analysis, see text. Since 2011, adjunctive clinical tests have proven useful in the diagnosis of LQTS. At four minutes after cessation of an exercise test, a QTc exceeding 480ms is highly suggestive of LQTS and is reflected in the Schwarz criteria. Likewise, QTc assessment at 10 seconds after standing shows a greater prolongation in those affected by LQTS when compared with unaffected individuals.

Keywords
Long QT syndrome • Diagnosis • Management • Genetics • Sudden death
Understanding of the diagnostic and risk stratifying role of LQTS genetics is discussed. At least 14 LQTS genes are now thought to be responsible for the disease. High-risk individuals may have multiple mutations, large gene rearrangements, C-loop mutations in KCNQ1, transmembrane mutations in KCNH2, or have certain gene modifiers present. In regards to treatment, nadolol is preferred and short acting metoprolol should not be used. Indications for ICD therapy are refined to (1) resuscitated cardiac arrest (2) recurrent arrhythmic syncpe whilst adherent to beta blockers, see text for relative indications. An emerging primary indication is post pubertal women with long QT type 2 and a QTc >550ms.

### Clinical Diagnosis

The diagnosis is usually made on clinical grounds, see Table 1, [2,3] and is suggested if the presentation is with syncpe or resuscitated sudden cardiac death, particularly if associated with exercise, sudden emotional stress, loud noise, or when supine. Prodromal symptoms of pre-syncpe, palpitations or a change in temperature can be experienced [4]. Syncpe associated with swimming should be suspected to be LQTS (or CPVT; catecholaminergic polymorphic ventricular tachycardia) until proven otherwise. Misdiagnosis of LQTS as epilepsy, particularly “familial epilepsy”, is common [5]. Seizures during exertion or arousal, and during sleep, must raise the suspicion of LQTS.

Differentiation from neurocardiogenic syncope is usually made on history. Neurocardiogenic syncope typically follows pain or prolonged upright posture, has a long prodrome and is associated with nausea [6]. Ambulatory event monitoring or implantable loop recorder can be valuable in detecting or excluding arrhythmia at time of syncpe if other tests are inconclusive. A family history of sudden unexplained death in young people is highly suggestive [6].

Studies of the three most common genotypes (Types 1, 2 and 3) have shown that the life-threatening cardiac events (syncpe or sudden death) tend to occur under specific circumstances in a gene-specific manner and have characteristic T wave morphologies [7], see Table 3. Subjects with long QT types 1 and 2 tend to have several “warning” syncopal episodes before a sudden death, whereas in long QT3 the first presentation is typically sudden death [8].

### Electrocardiographic Diagnosis

Abnormal ventricular repolarisation is demonstrated through QT prolongation or abnormal T-wave morphology on an incidental ECG or during family screening following a sudden unexplained death [9,10]. QT prolongation due to drugs or biochemical imbalance (low potassium, calcium or magnesium), hypothermia and myocardial disease must be excluded.

Despite the failings of the Bazett heart-rate correction formula (QT divided by square root of preceding R-R interval), it is still in popular use. The end of the QT interval is determined by extrapolating the steepest curve of the T wave down to the baseline [11]. Take the longest measurement of lead II or V5 [12]. Individuals with LQTS can have a normal QTc and vice versa [13,14]. Heart Rhythm Society guidelines suggest that, outside of family cascade screening, in asymptomatic individuals a QTc of ≥500ms on two separate ECGs is required to make the diagnosis of LQTS, but in patients with unexplained syncpe, the diagnosis can be made from QTc ≥ 480 ms on repeated ECGs [15].

Holter recordings are of limited additional value for making the diagnosis unless torsades de pointes or T-wave alternans is documented (which is very rare), or there is a history suggesting nocturnal events.

Exercise testing can be helpful. In the recovery phase following exercise, QT intervals of LQTS mutation carriers and non-carriers tend to separate more than at rest. An absolute QT interval of over 0.37 sec at a heart-rate of 100 post exercise is highly suggestive of LQTS types 1 or 2; a QT below 0.34 sec makes it unlikely [16]. QTc prolongation at four mins post exercise >480ms gains 1 Schwartz score point [17,18]. Normative values for children are available [19].

Examination of QT interval in the moments after standing can indicate LQTS carriage [20]. With the patient supine and 12-lead ECG monitoring, the patient briskly stands and within 10 secs, heart-rate increases (i.e. RR interval

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### Table 1: Diagnostic Criteria for LQTS (Schwartz Score)

<table>
<thead>
<tr>
<th>Electrocardiographic findings*</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>A QTc&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>≥480 ms</td>
<td>3</td>
</tr>
<tr>
<td>460-479 ms</td>
<td>2</td>
</tr>
<tr>
<td>450-459 ms (in males)</td>
<td>1</td>
</tr>
<tr>
<td>B QTc&lt;sup&gt;a&lt;/sup&gt; 4th minute of recovery</td>
<td>1</td>
</tr>
<tr>
<td>from exercise stress test ≥480 ms</td>
<td></td>
</tr>
<tr>
<td>C Torsade de pointes*</td>
<td>2</td>
</tr>
<tr>
<td>D Notched T wave in 3 leads</td>
<td>1</td>
</tr>
<tr>
<td>E Low heart rate for age@</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical History</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A Syncope*</td>
<td></td>
</tr>
<tr>
<td>With stress</td>
<td>2</td>
</tr>
<tr>
<td>Without stress</td>
<td>1</td>
</tr>
<tr>
<td>B Congenital deafness</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Family History</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A Family members with definite LQTS$</td>
<td>1</td>
</tr>
<tr>
<td>B Unexplained sudden cardiac death age 30 among immediate family members$</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*In the absence of medications or disorders known to affect these electrocardiographic features:  QTc calculated by Bazett’s formula where QTc=QT/√RR; *Mutually exclusive; @Resting heart-rate below the 2nd percentile for age; $The same family member cannot be counted in A and B.

Score: ≤1 point: low probability of LQTS; 1.5 to 3 points: intermediate probability of LQTS; ≥3.5 points high probability.
decreases). In those affected by LQTS, the QT interval reduces much less than the RR interval (there is less than a 20ms change in absolute QT). Therefore, at maximal QT stretch (where the end of the T-wave is closest to the next P-wave (i.e. the RR has shortened without the QTc adapting and shortening)) the QTc increases by 89±47ms and ventricular ectopic beats or T-wave alternans may be seen. In comparison, in those without LQTS, QTc increases by 50±30ms (P<0.001) [20]. This is a relatively new test requiring validation in other cohorts, and there is a paucity of normative data, especially in children, so while it may add value, it is prudent to be cautious in interpreting these results.

**Family History**

A detailed family history looks for a history of syncope or sudden unexplained death at a young age 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. Any sudden unexpected natural death with a negative post-mortem should trigger a family investigation for LQTS and other channelopathies.

**Family Screening**

Once the diagnosis is suspected, ECGs should be obtained on all first-degree relatives. QTc values of ≥440ms are treated as suspicious and values below 410ms are uncommon in gene carriers. Up to one third of asymptomatic gene mutation carriers have QTc values within the normal range [21]. Therefore, examining T-wave morphology, reviewing QT interval behaviour after exercise testing and performing genetic testing are important adjuvants. 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 have 50% chance of passing on the mutation to each of their children.

**Molecular Genetics**

**Familial LQTS Disease Genes**

LQTS is caused by mutations in any of 15 LQTS genes (Table 2), with the number of genes expected to keep rising with further studies. The most common pattern of inheritance is autosomal dominant (sometimes called Romano-Ward syndrome) which is caused by a single mutation in any of these genes. Each child of an affected parent has a 50% chance of inheriting a disease-causing gene mutation.

The most common genotypes are types 1 and 2; next in frequency are types 3 and 5 [22]. In each, a dysfunctional cardiac ion-channel results in prolongation and/or distortion of the cardiac action potential, and thus the QT interval and T wave. Many of the hundreds of mutations found to date are unique to a family or very rare; and detail about pathogenicity may be lacking. About a quarter of families with LQTS do not yet have a recognised genetic locus. Test yield and interpretation are best when clinical phenotype is well established in the proband.

Two recently described new syndromes seem at this stage to be very severe and affect only young children, the so-called

<table>
<thead>
<tr>
<th>Clinical name</th>
<th>Chromosomal locus</th>
<th>Gene name</th>
<th>Current Affected</th>
<th>Proportion of mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>11p15.5</td>
<td>KCNQ1 (KVLQT1)</td>
<td>K+ (IKs)</td>
<td>38%</td>
</tr>
<tr>
<td>LQT2</td>
<td>7q35-36</td>
<td>HERG (KCNH2)</td>
<td>K+ (IKr)</td>
<td>42%</td>
</tr>
<tr>
<td>LQT3</td>
<td>3p21-24</td>
<td>SCN5A</td>
<td>Na+ (INa)</td>
<td>12%</td>
</tr>
<tr>
<td>LQT4</td>
<td>4q25-27</td>
<td>Ankyrin B</td>
<td>Na+ (INa)</td>
<td>1%</td>
</tr>
<tr>
<td>LQT5</td>
<td>21q22.1-22.2</td>
<td>KCNE1 (minK)</td>
<td>K+ (IKr)</td>
<td>5%</td>
</tr>
<tr>
<td>LQT6</td>
<td>21q22.1-22.2</td>
<td>KCNE2 (MiRPI)</td>
<td>K+ (IKr)</td>
<td>1%</td>
</tr>
<tr>
<td>LQT7 (Anderson)</td>
<td>17q23</td>
<td>KCNJ2</td>
<td>K+ (INa)&lt;0.1</td>
<td></td>
</tr>
<tr>
<td>LQT8 (Timothy)</td>
<td>12p13.3</td>
<td>CACNA1C</td>
<td>Ca++ (ICa-L)&lt;0.1</td>
<td></td>
</tr>
<tr>
<td>LQT9</td>
<td>3p25</td>
<td>CAV3 (Cavedin)</td>
<td>Na+ (INa)&lt;0.1</td>
<td></td>
</tr>
<tr>
<td>LQT10</td>
<td>11q23.3</td>
<td>SCN4B</td>
<td>Na+ (INa)&lt;0.1</td>
<td></td>
</tr>
<tr>
<td>LQT11</td>
<td>7q21-q22</td>
<td>AKAP9 (A-anchor protein 9)</td>
<td>K+ (INa)&lt;0.1</td>
<td></td>
</tr>
<tr>
<td>LQT12</td>
<td>20q11.2</td>
<td>SNTA1 (alpha-1 syntrophin)</td>
<td>Na+ (INa)&lt;0.1</td>
<td></td>
</tr>
<tr>
<td>LQT13</td>
<td>11q24.3</td>
<td>KCNJ5</td>
<td>K+ (Ko)&lt;0.1</td>
<td></td>
</tr>
</tbody>
</table>

*From Modell, 2006 [63].

Calcium channel, voltage-dependent, L type, alpha 1C subunit.

LQT7-Anderson syndrome is a rare neurological disorder characterised by periodic paralysis, skeletal developmental abnormalities, and QT prolongation.

LQT8-Timothy syndrome is a rare condition characterised by syndactyly, facial dysmorphism, autism and severe LQTS.

Two further LQT types are referenced in the text; due to mutations in Calmodulin and Triadin.
triadin-knock out syndrome with recessive inheritance, and Calmodulin related disease [23,24].

Determination of genotype can be useful to confirm diagnosis, allow genetic screening of potentially affected family members and tailor therapy. Certain mutations can identify individuals at higher risk, and due to genotype-phenotype correlation (see Table 3), gene (and even mutation)-specific risk avoidance and therapy can be instituted after genotyping has been performed.

Genetics of Special Note

Multiple Mutations
Approximately 5% of families have two mutations, and family members with both mutations tend to be more severely affected. The presence of two mutations on opposite chromosomes 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) [25] low gastric acid secretion and iron deficiency anaemia are also features of this rare condition [26].

Large Gene Rearrangements
Secondary testing for deletions and duplications of exons should be considered in the group of patients who are definitely and severely affected by LQTS yet standard genetic testing was uninformative. Deletions and duplications have been identified in 5-15% of such individuals [27,28].

C-loop Mutations in KCNQ1 (LQT1) at Residues 171 to 195 and 242 to 262
Patients with missense mutations in the cytoplasmic loops of KCNQ1 are at the highest risk of cardiac events (regardless of other risk factors), generally triggered by exercise. However, their risk is also most significantly reduced by the use of beta blockers, so this therapy is particularly important here [29].

SCN5A
Mutations in the cardiac sodium channel gene SCN5A, cause long QT type 3 if the cardiac sodium channel (Na,v1.5) is overactive (leaking sodium and prolonging the action potential), and cause Brugada syndrome if it is underactive [30]. Both clinical conditions tend to cause nocturnal sudden death as their first symptom, and families exist where both of these conditions are present in different family members, with the same genetic mutation. Among LQTS related sudden unexpected death in infancy and 1-40 year olds, SCN5A mutations are the most common [31].

Gene Modifiers
Modifiers of gene expression have been identified and show promise as potential tools to assess risk. They include untranslated regions which modify the RNA binding site in LQT1 [32] and minor changes (single nucleotide polymorphisms) in NOS1AP, a gene linked to QT prolongation in the general population [33].

Genetic Screening

The main value of genetic testing lies in family screening. Following the identification of a proband with unequivocal LQTS, molecular diagnosis is then sought through screening the known LQTS genes in the affected individual. Once the disease causing mutation is identified, screening for this specific mutation in the family is relatively quick and inexpensive.

Careful counselling prior to testing is essential (particularly if the individual is clinically unaffected). Negative aspects of a positive genetic diagnosis include potential insurance, employment and psychological problems. Input from a cardiac-genetic counsellor is beneficial, especially when the genetics of LQTS is outside the clinicians’ usual scope of practice [35].

Interpretation of genetic results is best performed with input from molecular and clinical genetics.

Genetic screening for LQTS as part of a molecular autopsy in autopsy-negative young sudden death can reveal a diagnosis in 15-20% of cases [31,36].

Table 3 Phenotypic characteristics of LQT types 1,2 and 3

<table>
<thead>
<tr>
<th>LQT type</th>
<th>T-wave morphology</th>
<th>Events triggered by exercise (%)</th>
<th>Events triggered by excitement (%)</th>
<th>Events during rest or sleep (%)</th>
<th>Reduction of risk of SCD by beta blockers</th>
<th>Group most severely affected</th>
<th>Percentage of LQT gene positive SUDI cases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Broad based</td>
<td>62</td>
<td>26</td>
<td>3</td>
<td>75%</td>
<td>Boys aged 5-15</td>
<td>10%</td>
</tr>
<tr>
<td>2</td>
<td>Low voltage, double bump</td>
<td>13</td>
<td>43</td>
<td>29</td>
<td>50%</td>
<td>Adult women</td>
<td>10%</td>
</tr>
<tr>
<td>3</td>
<td>Late onset high amplitude</td>
<td>13</td>
<td>19</td>
<td>39</td>
<td>No established benefit</td>
<td>Adult male and infants</td>
<td>68%</td>
</tr>
</tbody>
</table>

*SUDI, sudden unexplained death in infancy.

Management

Affected Individuals

Removal of Triggers
All gene carriers must avoid medications which prolong the QT interval, can cause torsade de pointes or lower serum potassium or magnesium levels. A constantly updated list is available at www.crediblemeds.org. Herbal remedies and
some dietary treatments also represent a risk [37]. Secondary triggers such as hypokalaemia and medications are especially common in adults [38].

**Lifestyle Modifications**

With all forms of LQTS, where there is a long QT interval (and not necessarily just gene carriage), a degree of caution with sporting activity is recommended. There is increasing evidence that the risk is low if patients adhere to beta blocker therapy [39]. With LQT1, and subjects with a history of exercise induced syncope, swimming and diving are generally contraindicated. However, many patients choose to continue with swimming, and these are sometimes managed by the use of an advisory defibrillator with a supervisor at the pool-side, and adjuvant cardiac sympathectomy may be used. Exercise precautions are more imperative with LQT1, or in those who have already experienced events during exercise, than in LQT2 and 3. Such individuals should generally be advised away from becoming professional athletes. With LQT2, or those with a history of auditory evoked events, removing loud alarm clocks and turning down the volume on the phone at night is advisable.

**Assessing Level of Risk of Sudden Cardiac Death**

Management must be guided by an assessment of risk. Approximately half of LQTS gene carriers never have a symptom. Table 4 shows risk factors derived from data from the international long QT registry.

Whilst exercise testing can help clarify gene carriage, there is as yet no evidence supporting the use of such recordings to assess risk. Although the death of a family member may understandably bring a perception of increased risk, there is no evidence that it does [40,41]. Careful evaluation has demonstrated, for example, that death of a sibling does not increase risk [41].

**Beta Blockade**

Beta blockade should be initiated in those who have had symptoms, or those with a QTc > 470ms, [15] particularly in pre-adolescent boys, including infants. For those with a normal QTc, the decision regarding beta blockers is individualised. Overall reduction of risk of sudden cardiac death by beta blockers in high risk subjects is 67% in LQT1 males and 71% in LQT2 females [42]. This effect may be even higher if long-term compliance is assured [43]. No benefit is yet firmly established with long QT 3, though it has been suggested to reduce risk to one third, particularly in women, by a multinational registry report, not yet in full publication [44]. Long-acting agents are preferred to aid compliance, such as nadolol. Short-acting (twice daily) metoprolol should not be used [45]. Nadolol may have a superior protective effect to other beta blockers in long QT type 2, and may be the most effective at preventing first cardiac events in LQT1 and LQT2, and propranolol may be least effective in those with prior cardiac events [46]. Up-titrating to the highest tolerated dose is advised. Once started, beta blockers should not be stopped suddenly; there is a period of high risk after cessation due to up-regulation of beta-receptors on treatment.

Among those receiving primary ICDs, women (post-pubertal females) with long QT type 2 and significant QT prolongation, are the most likely to receive an appropriate discharge [47].

LQT3 patients are at higher risk at slower heart-rates, and the QT interval shortens at faster heart-rates. This raises concerns regarding the use of beta blockers in this group. 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. Holter recordings in LQT3 are important since they may reveal gross QT and T wave changes with bradycardia, especially overnight. QT response to exercise is generally normal. LQT3 patients may benefit from pacemakers, which can also allow the safe use of beta blockers. There is a high mortality rate despite therapy even at the first episode, especially in males with a very long QT interval. Early placement of ICD has often been performed in asymptomatic subjects with a very long QT interval, but to date such primary prevention has seen very few appropriate ICD discharges, [47] but significant numbers of inappropriate discharges [48].

**Novel Medical Therapy**

No gene-specific therapies have proven effective in reducing risk of death, nor are they yet known to be safe. QT interval

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**Table 4  Assessment of clinical risk**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Risk relates to the longest QTc recorded [64] and increases as QTc length increases, especially when QTc exceeds 500ms [8]. An 18-year-old with a QTc&gt;550ms has a 19% chance of cardiac arrest by aged 40, compared with a 2% risk if the QTc is less than 470ms [65].</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc length on serial resting ECGs</td>
<td>A cardiac event, particularly in the last two years similarly identifies increased risk. LQT gene carriers, like the general population, may suffer from neurocardiogenic syncope. Risk stratification depends on correctly assigning the nature of the syncope.</td>
</tr>
<tr>
<td>History of arrhythmic syncope or cardiac arrest</td>
<td>Risk factors interact; for example, boys with LQT1 and women with LQT2 (particularly in the first post-partum year) are at particularly high risk [66]. A 6-year-old boy with a history of syncope has a 15% risk of cardiac arrest by age 12, compared with 0.6% risk in an asymptomatic 6-year-old girl [40].</td>
</tr>
</tbody>
</table>
can be shortened experimentally with potassium pump enhancing agents, such as nicorandil in LQT type 1, [49] or spironolactone combined with oral potassium in LQT type 2. [50] In LQT type 3 sodium channel blockers, such as mexiletine [51] or flecainide, can shorten the QT interval, but the latter may induce a Brugada phenotype [52]. Anecdotally mexiletine has successfully treated VT storm in LQT3, and is recommended by some practitioners when there is a very long QT interval [48].

Implantable Cardioverter-defibrillator (ICD)

**ICD therapy in LQTS is indicated for**

1. Resuscitated cardiac arrest (Class I indication) [15,53]
2. Recurrent arrhythmic syncope whilst on beta blockers (Class IIa indication) [15,54]

**Relative indications for ICD insertion include when**

1. Beta blockers are contra-indicated and high risk is established [15] or
2. The QT interval is very long (QTc>0.55 sec) even without symptoms, particularly adult females with LQT2, and patients with a double mutation [25].

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.

Despite the ICD’s efficacy at preventing sudden death, [54] patients should be carefully selected due to the morbidity associated with ICD placement in this young cohort [55]. This is of particular importance when the device is placed for primary prevention where the risk of serious harm from ICD placement may exceed benefit [55]. In addition to issues with inappropriate shocks, need for revisions, lead dislodgement/fracture and change in capture/sensing/defibrillation thresholds, [47,56] careful and considered programming is required to prevent inappropriate cardioversions due to tachy- and brady-arrhythmias or ventricular tachycardia which would likely self-terminate [57]. Subcutaneous ICD systems should be considered if there is no indication for pacing, as these systems avoid the risks associated with transvenous leads.

**Left Cardiac Sympathetic Denervation (LCSD):**

**Minimally invasive left cardiac sympathectomy** [58,59] may be considered for

1. Those with severe disease and in whom beta blockers are contra-indicated or ICD cannot be placed or is not wanted.
2. Controlling VT storms (or increasing the VF threshold) in those with an ICD, including repeated discharges in those already on beta blockers.
3. LQT3 or a personal or family history of events during rest or sleep.

Some individuals at intermediate risk may choose this option rather than take beta blockers, and it may be considered as a primary prevention when adherence is likely to be poor and particularly in boys with LQT1. Those at high risk should continue beta blockers after the sympathectomy when feasible. Pneumothorax and left ptosis are uncommon complications when performed using video-assisted thoracic sympathectomy. Asymmetrical facial flushing and sweating is more common, as is dryness of the left hand and profuse sweating of the right hand [60].

**Asymptomatic Family Members**

When a familial disease-causing mutation has been identified, testing family members can reveal those who are affected (gene positive) and those who are not (gene negative). In those who are gene negative for the family mutation, they are considered not at risk of LQTS, will not have affected children, and do not require any special management. They (and their dependents) should be released from follow-up, but retention of their information in a registry allows further communication if required.

For those family members who are genotype confirmed, but are asymptomatic, some risk reduction is warranted. Regardless of QTc length, all individuals should avoid medications contra-indicated in LQTS. Those with a long QT interval (>500ms), especially young males and adult females need to be treated much as someone who has already presented with syncope. Beta blockers should be proposed and sensible precautions placed on sporting activities, particularly swimming.

The role of beta blockers in those without symptoms, a normal QT interval yet a positive genetic diagnosis is controversial. Intuitively, those with a family history of adrenergic induced cardiac events or known to have LQT1 are most likely to benefit. Risk of life threatening arrhythmia is 4% by age 40 years in this group. This compares to 0.4% in gene negative family controls. However two-thirds of these subjects had warning syncope prior to potentially lethal arrhythmia, and thus would, under appropriate surveillance, have been started on therapy. Death under age 10 is very rare (one LQT3 infant among 3,386 genotyped subjects) [61]. It was demonstrated that gene carriers with a normal QT interval who had mutations in the transmembrane region of LQT1 (KCNQ1) or LQT3 (SCN5A) have a six-fold higher risk of serious arrhythmia or death than other mutations in those with a normal QT interval [61].

It should be remembered that intermittent adherence to beta blocker therapy may carry its own risk; when the medication is stopped, the up-regulated beta-receptors may lead to an increased risk for a few days after cessation. Current opinion thus suggests that in a subset of patients beta blockers might be reasonably withheld [62]. Such an approach should only be taken after informed discussion with the patient or family. The group concerned are asymptomatic and have a repeatedly normal QT interval, and do not have a missense c-loop KCNQ1 mutation [61]. Among this group, pre-pubertal females are particularly low risk. This approach implies detailed knowledge of the genotype, and does not imply that subjects should be discharged from expert cardiological follow-up. They must all avoid QT prolonging medications.
Genetic Counselling and Psychological Counselling

The main aim of the clinician is to prevent sudden death. A secondary aim is to assist the family in their adjustments that have to be made. Dedicated professional assistance should be offered when appropriate by clinical psychologists and genetic counsellors. Genetic counselling is particularly important prior to testing an asymptomatic individual with a normal ECG. A positive result may have adverse psychological, social, employment and insurance effects.

Some of those at highest risk from psychosocial issues are adolescents and teenagers. Beta blocker therapy and the limitations on activities can be met with resistance. Appropriate counselling may assist patients to feel some retention of control in their life whilst still taking steps to minimise their risk.

Further Information

Inherited Heart Disease Clinics are growing in number. Local coordinators can give advice regarding genetic testing.

Useful Websites

www.sads.org (International site of the Sudden Arrhythmia Death Syndromes Foundation)
www.sads.org.au (Australian site)
www.cidg.org (Cardiac Inherited Diseases Group, New Zealand)
www.crediblemeds.org (Medications which prolong the QT interval)

Conflicts of Interests

There authors have no conflicts of interest to declare.

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