involves taking beta-blocker medications daily (preferably nadolol or propranolol). This approach is effective for the majority of patients with LQTS. The dose needs to be monitored closely, balancing the prevention of LQTS spells with unwanted side effects related to decreased energy level and altered mood.

Patients who continue to have symptoms in spite of appropriate doses of beta-blockers, or are not able to tolerate their beta-blocker therapy, may need either additional medications, surgery (left cardiac sympathetic denervation [LCSD]), or device therapy with an implantable cardioverter defibrillator (ICD). Patients who have experienced a cardiac arrest usually receive an ICD. With LQTS genetic testing, treatment strategies can be guided by the underlying genetic cause. For example, beta-blockers are extremely protective for most patients withtype 1 LQTS (LQT1) and are also protective for the majority of patients with type 2 and type 3 LQTS (LQT2 and LQT3). LCSD surgery is available in a few LQTS specialty centers providing another important treatment option for those patients who continue to have syncope despite beta-blockers, or have experienced appropriate ICD shocks or are not tolerating their medications because of excessive side effects.

Persons over 40 years of age at the time of diagnosis (perhaps > 25for men with LQT1) who have been asymptomatic (without symptoms) all their life (or for many, many years) may not need any active treatment, as their risk of developing symptoms at later ages is very low. As with all patients with LQTS, these seemingly low-risk older patients need to avoid low blood potassium (caused by diuretic drug use, vomiting or diarrhea) and avoid (whenever possible) those drugs which aggravate the heart's recharging system and prolong the QT interval. This combination of an otherwise dormant LQTS genetic substrate plus a 'second hit' can provide a fatal 1-2 punch. For a complete list of drugs that prolong the QT interval and/or induce torsade de pointes, visit StopSADS.org or crediblemeds.org.

Medication compliance

It is very important that LQTS-directed medical therapies be taken every day and not missed or omitted. The medications are not curative; they only provide protection while being taken and depending on the beta blocker, the protective effect can disappear within a day. After that the risk of cardiac events is the same as if the patient had not taken the medication at all. In addition, dose skipping/missing can actually be dangerous as the heart can become hyperexcitable when the medicine is not present. Parents should teach their children about the importance of daily medication, and should make sure each daily dose is taken. Physicians need to discuss this directly with all patients, but particularly pre-teens and teenagers. **The most common reason for cardiac events while on medication may be that the medication was missed or stopped**.

How can parents protect their kids?

- Make sure the children take their medication daily, no missing doses.
- See the doctor regularly for follow-up. Growing children need medication dose changes regularly. Make sure you see the doctor at least once a year, more frequently during very rapid growth, and discuss the need for dose changes. These drugs are given according to body weight; so, in growing children dose changes may be frequent.
- If your child has a passion for sports, your child should be evaluated by a physician with expertise in LQTS to determine if continuation in competitive sports is reasonable.
- Get additional medical advice if you are not comfortable with how things are going. Ideally, every patient/family with LQTS should be cared for by a heart rhythm specialist (pediatric or adult cardiac electrophysiologist) or even a long QT syndrome specialist. Do not hesitate to obtain a second opinion if you have any questions about your or your child's treatment.
- Learn CPR, encourage your child's school district to implement an automatic external defibrillator (AED) in their schools, and consider obtaining a personal AED as part of the family's LQTS safety gear. However, when well treated, remember that the AED should almost never be required.
- It is important to be sure that your child's school is aware of his or her condition and is properly prepared to respond in the event of an emergency. Visit StopSADS.org for care plans and other important materials that will help you in meeting with school personnel to ensure a safe environment for your child.
- At the appropriate time, your child should also be informed that they can and should become a mother or father someday if they want to. Any recommendations that they should not become a parent because of their LQTS should be viewed as inappropriate nonsense. Pregnancy and delivery can be navigated successfully and relatively simply in women with LQTS but will require a teamwork approach between your LQTS specialist and the obstetrician.

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Congenital Long QT Syndrome (LQTS)

A Guide for Patients and Health Care Providers

SADS FOUNDATION

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Why do I need to know about congenital long QT syndrome (LQTS)?

We estimate that at least 1 in 2000 people in the United States have congenital long QT syndrome (LQTS). LQTS-triggered sudden deaths continue to claim otherwise healthy infants, children, adolescents, and adults at an unacceptably high rate. However, with increased awareness, genetic testing, and effective treatment options, LQTS can be diagnosed early and sudden death prevented. Still, this condition is often undetected prior to death and not recognized as the cause of death. Family members of individuals with unexplained death should be tested for the possible presence of LQTS and other genetic arrhythmias. If an inherited condition like LQTS was responsible for the unexplained death, then 50% of family members may also be affected. LQTS is a highly treatable disorder and, with correct diagnosis and common treatments, most deaths are preventable. Currently, annual mortality for properly treated patients is less than 1%.

Physicians need to know:

- When to consider LQTS as a possible diagnosis.
- When to refer patients for diagnosis & treatment.
- About genetic testing for LQTS and other SADS conditions.
- How to develop a family pedigree and screen family members for LQTS.

What is LQTS?

LQTS is a disturbance of the heart's electrical system. It is caused by abnormalities of microscopic pores (proteins) in the heart cells called ion channels. Ions such as potassium, sodium, calcium and chloride pass back and forth across the cell membrane through ion channels. As they do, these ion channels generate the electrical activity (depolarization and repolarization) that controls the heart's beating. Our window to this electrical activity of the heart is through an electrocardiogram (ECG). Potassium and sodium ion channels are two types of ion channels affected in LQTS. The abnormal channels prolong the repolarization ("recharging") process and the QT interval, thus predisposing patients to certain cardiac arrhythmias. Thus, LQTS can be thought of as a glitch in the electrical recharging phase of the heart.

What is the QT interval?

The QT interval is a time interval on the ECG. It represents the time from the electrical stimulation (depolarization) of the heart's pumping chambers (ventricles), to the end of the recharging of the electrical system (repolarization). It is measured in milliseconds and closely approximates the time from the beginning of the ventricles' contraction until the end of relaxation.

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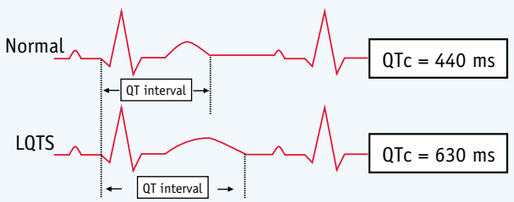
The QT interval varies in each person and between persons like most physiologic parameters, such as blood pressure or heart rate. In particular, the QT varies with the heart rate. It shortens as the rate increases and lengthens as the rate decreases. Therefore, there is a range of normal or healthy QT intervals. In contrast, the long QT heart often recharges sluggishly or inefficiently as evidenced by a "prolonged QT interval" on the ECG.

To determine if a given QT is normal for a given heart rate, the QT is corrected for the heart rate using a simple mathematical formula, and the resultant quantity is called the heart-rate corrected QT interval or the QTc. The QTc is the value that doctors generally use when assessing for LQTS.

The average QTc value is around 400 +/- 20 ms. Probably less than 1% of the population has a QTc < 350 ms and less than 1% has a QTc > 480 ms. About 90% of people have a value between 380 ms and 440 ms, which is the range doctors generally consider as the ˝normal˝ range. However, this "normal" range is affected by age, particularly relevant in children, and gender. For example, women tend to have slightly longer QTc values then men. While a QTc of 440 ms represents the top 2.5 percentile in a 4-day old infant, this same QTc value is seen in 10 – 20% of postpubertal women. The diagram below provides an example of a normal and a prolonged QTc.



What are the symptoms of LQTS?

Over half of all patients diagnosed with LQTS NEVER have a symptom. However, if/when the LQTS heart "spins electrically out of control" in its trademark cardiac arrhythmia (called torsade de pointes), sudden, temporary, loss of consciousness (syncope) is the most common event. These events usually occur without warning and are often triggered by exertion or auditory stimuli. Typically, the onset of symptoms is earlier in boys than in girls. Statistically, the greatest risk window includes the first three decades of life (the first two decades in males and the second and third decade in females). However, there are tragic exceptions to these trends and LQTS-related events can continue in people in their 40s,50s, and beyond. When presenting later, a second hit, due to a medication that further aggravates the QT interval or low potassium, is often present and helps create the "perfect storm" for the otherwise silent LQTS substrate to rear its head.

In patients who experience syncope only, the torsade de pointes rhythm spontaneously returns to normal, usually in less than a minute, and the patient quickly regains consciousness, without disorientation or confusion. Some patients may experience slight fatigue afterwards; others feel fine and resume their regular activities. If this bad LQTS rhythm persists longer, patients may then manifest a generalized seizure. In fact, some patients with LQTS have been misdiagnosed initially with epilepsy and even treated with anti-epileptic medication. In both the syncope and seizure presentations, the long QT heart reverted back to normal sinus rhythm, and the "spell" is over. On the other hand, in a minority of patients, the torsade de pointes rhythm persists longer still and degenerates further into the heart rhythm known as ventricular fibrillation, which rarely reverts back to a normal rhythm without medical intervention. If the ventricular fibrillation is not (immediately) converted by electrical defibrillation from an automatic external defibrillator (AED) or occasionally by a precordial thump, the outcome is sudden cardiac death.

When should the diagnosis be suspected?

- In any young person with **unexplained syncope (fainting), unexplained seizures, or unexplained cardiac arrest or sudden death.**
  Usually, a careful history of the events surrounding the syncope differentiates LQTS-induced syncope from the common faint, known as vasovagal or neurocardiogenic syncope. The LQTS faint is usually precipitous and without warning. It often occurs during or just after **physical exertion (including swimming), emotional excitement including fear or sudden auditory arousal** (such as a doorbell or alarm clock), but may occur during sleep or at rest. Conversely, in vasovagal syncope, most times there are warning symptoms, such as dizziness, blurring or blackening of vision, tingling or sweating, for seconds to even minutes prior to the syncope. Also, a precipitating event is usually present, commonly pain, injury, nausea, or an unpleasant or stressful experience.
- When there is a **family history** of unexplained syncope, unexplained seizures, or sudden death in young people. As noted above, at least over one-half of all individuals diagnosed with LQTS never exhibit symptoms, and, therefore, the lack of prior symptoms does not exclude a person or family from having LQTS.
- When the autopsy is normal following the sudden and unexpected death of a young person.

How is the diagnosis made?

LQTS is suspected based upon the patient's personal story, his/her family story, and careful examination of the ECG. If the story is suspicious, a QTc exceeding 470 ms in males and 480 ms in females is sufficient evidence for a diagnosis of probable LQTS, assuming that medications which prolong the QT interval or other QT-prolonging medical conditions have been ruled out. Importantly, as an incidental ECG finding, QTc values exceeding these cut-off values do NOT equal the diagnosis of LQTS. On the other hand, a QTc of less than 400 ms in males and 410 ms in females makes the diagnosis unlikely. **The computer generated QTc often is incorrect, so when the diagnosis of LQTS is considered, the physician must confirm manually the QTc measurement.**

However, not all LQTS patients have a prolonged QTc on the initial ECG. In fact, about 30 – 50% have a QTc that overlaps with the normal range and at least 25% of affected relatives have a QTc < 440 ms. QTc's in this range are inconclusive, and therefore, the possibility of LQTS must be clarified by repeating the 12-lead ECG, obtaining ECGs on first degree relatives, regular or 12-lead 24 hour Holter monitoring, bicycle or treadmill stress testing, and and genetic testing. When these additional tests are necessary to unmask or catch LQTS, all the tests must be interpreted carefully because of the potential for false positives.

How is LQTS inherited, and who in a known or suspected family should be tested?

LQTS is usually inherited by autosomal dominant transmission. This means that it generally affects boys and girls equally, and that each child of an affected parent has a 50% chance of inheriting the genetic abnormality. In a really large family, close to 50% of the children would inherit the LQTS-causing genetic abnormality. In average size families, it can range from all to none as each child has an independent 50/50 chance (like a coin-toss) of inheriting the particular disease gene. Once a family member is identified with LQTS, it is extremely important that other family members be tested for the syndrome. It is especially important to know which parent and grandparent has the abnormality, since brothers and sisters, aunts, uncles, nephews, nieces, and cousins on the affected side are potentially at risk.

This initial family/relative screening, by ECG, is extremely important so that all affected family members are identified and treated early in order to prevent the tragic and unnecessary sudden deaths that may otherwise occur. Importantly, however, once the diagnosis of LQTS has been established firmly in the family, there is no QTc value on the ECG that can be viewed as reassuring enough to dismiss the relative. If the genetic test is positive for the index case/proband, only cascade genetic testing of the family members that yields a negative genetic test result AND a normal ECG can enable that family member to be dismissed as unaffected.

What about genetic testing?

Genetic testing for LQTS is now the "standard of care" and it is increasingly being used to confirm the diagnosis of LQTS, assist in risk stratification, and guide the patient's treatment program As mentioned above, it will also help your family members to get diagnosed and treated. For people with a "borderline" diagnosis because your QTc is almost normal and they have no symptoms, genetic testing can help the physician "move away" from the diagnosis of LQTS or "move towards" the diagnosis of LQTS.

Your physician will order the initial test on one family member (so-called index case). Once/if a family member has a LQTS-causative pathogenic variant/likely pathogenic variant identified, testing of other family members for that specific genetic variant is available, and can assist in clarifying those family members with non-definitive ECG findings. In fact, if a genetic diagnosis of LQTS is established for the index case, the ONLY definitive test to rule in or rule out LQTS for family members and relatives is the LQTS genetic test. It is also very reassuring to know that certain members of the family are not affected and that, therefore, they will not transmit the disease to their offspring.

There are a number of commercial, CLIA-certified labs from which you can order your genetic testing. As with any healthcare service, it is always a good idea to be a wise consumer and research each company to see which one might be the better choice for you. Visit StopSADS.org for more information.

What is the treatment and who should be treated?

All **symptomatic** patients should receive treatment. Most children and young adults should be treated even if they do not have symptoms. This is because symptoms might occur and sudden death can be the first symptom. At present, it is not possible to tell which child or youth is destined to have symptoms. Thus, preventive treatment is recommended for most. The usual treatment