patients who continue to have syncope despite beta-blockers, have experienced appropriate ICD shocks, or are not tolerating their medications because of excessive side effects.

With LQTS genetic testing, treatment strategies can be guided by the underlying genetic cause. For example, beta-blockers are generally extremely protective in type 1 LQTS (LQT1) and for most patients with type 2 and type 3 LQTS (LQT2 and LQT3). Mexiletine (a heart medication) may also be used along with beta-blockers in LQT2 and LQT3.

Persons over 40 years of age at the time of diagnosis (perhaps > 25 for LQT1 males) 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 drugs that 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

LQTS-directed medical therapies must be taken every day and not missed or omitted. The medications are not curative; they only protect 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 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 should 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 has been missed or stopped**.

How can parents protect their kids?

- Make sure the children take their medication daily, with no missing doses.
- See the doctor regularly for follow-ups. 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 uncomfortable with how things are going. Ideally, every patient/family with LQTS should be cared for by a heart rhythm specialist (cardiac electrophysiologist) or long QT syndrome specialist. Do not hesitate to obtain a second opinion if you have questions about your or your child's treatment.
- Learn CPR, encourage your child's school district to have 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 prepared to respond in the event of an emergency. Visit StopSADS.org for care plans and other important materials to help you when 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 against becoming a parent because of their LQTS should be viewed as inappropriate. 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. Sleep disruption in the postpartum period should be avoided in LQT2 mothers, as this is a period of increased arrhythmic risk, with partners helping to feed the infant during the nighttime. Some families may wish to discuss family planning options with a genetic counselor to understand all options available to them, including in vitro fertilization.

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The Long QT Syndrome

A Guide for Patients and Health Care Providers

SADS FOUNDATION

StopSADS.org

Why do I need to know about the Inherited Long QT syndrome?

An estimated 1 in 2000 people in the United States have LQTS. LQTS-precipitated 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 before death and not recognized as the cause of death. Family members of individuals with unexplained death should be tested for 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 treatable, and with correct diagnosis and common treatments, most deaths are preventable. Currently, mortality for properly treated patients is close to 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 in 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 by LQTS. The abnormal channels prolong the repolarization ("recharging") process and the QT interval, thus predisposing patients to certain cardiac arrhythmias. Thus, LQTS is a glitch in the electrical recharging phase of the heart.

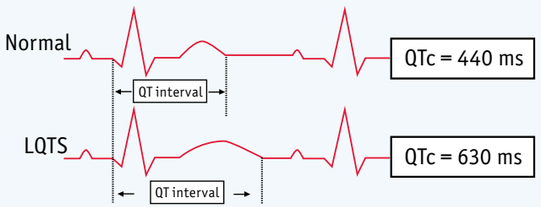
What is the QT interval?

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.

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 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 in children, and gender. For example, women tend to have slightly longer QT intervals than 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?

Nearly half of patients 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, emotional stress, 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 decades in females). However, there are tragic exceptions to these trends, and LQTS-related events can continue in people in their 40s and 50s. When presenting later, a second hit, due to a medication that further prolongs the QT interval or low potassium, is often present.

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 afterward; 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 to normal sinus rhythm, and the "spell" was over. In a minority of patients, the torsade de pointes rhythm persists longer and degenerates further into the heart rhythm known as ventricular fibrillation. This rhythm rarely reverts to a normal rhythm without medical intervention. If the ventricular fibrillation is not (immediately) converted, usually by electrical defibrillation, the outcome is sudden cardiac death or sudden cardiac arrest.

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 sudden 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 it 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 before 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 one-third to one-half of individuals never exhibit symptoms.* **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 on the patient's personal story, 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 that 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 is often incorrect, so when the diagnosis of LQTS is considered, the physician must manually confirm the QTc measurement.**

However, not all LQTS patients have a prolonged QTc on the initial ECG. 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 intervals in this range are inconclusive and must be clarified through exercise stress testing, 12-lead 24-hour Holter monitor, and genetic testing.

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 large family, nearly 50% of the children would inherit the LQTS-causing genetic variant. In average-size families, it can range from all to none as each child has an independent 50/50 chance of inheriting the particular disease gene. Other family members must be tested once a family member is identified with LQTS. It is especially important to know which parent and grandparent has LQTS since brothers and sisters, aunts, uncles, nephews, nieces, and cousins on the affected side are potentially at risk.

This screening, by ECG and genetic testing, when the family's genetic variant is known, is crucial so all affected family members are identified and treated to prevent tragic and unnecessary sudden deaths.

What about genetic testing?

Genetic testing for LQTS is the "standard of care" for those diagnosed with LQTS, and it is increasingly being used to diagnose and appropriately treat people. It will also help your family members get diagnosed and treated. For people with a normal or almost normal QTc and who have no symptoms, genetic testing can help "rule out" or "confirm" your diagnosis of LQTS. Around 15% of people who have LQTS will have a negative genetic test result. This does not rule out LQTS in someone who has been clinically diagnosed based on their ECG and other testing.

Your physician will order the initial test on one family member (so-called index case). Once/if a family member has a pathogenic (disease-causing) variant identified, other family members can be tested for that specific variant. This can clarify those family members with non-definitive ECG findings. 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 family members did not inherit the disease-causing variant, are not affected, and will not pass their condition to their children.

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 because symptoms might occur, and sudden death may 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 involves taking beta-blocker medications daily. This approach is effective for the majority of patients with LQTS. The dose needs close monitoring, balancing the prevention of LQTS spells with unwanted side effects related to energy level and mood.

Patients who continue to have symptoms despite appropriate doses of beta-blockers or are not able to tolerate their beta-blocker therapy may also require additional medications, surgery (left cardiac sympathetic denervation [LCSD]), or device therapy with an implantable cardioverter defibrillator (ICD). Patients who have experienced a cardiac arrest may receive an ICD, however, they may be started on beta-blockers and potentially have an LCSD first to avoid an ICD if they were untreated at the time of the arrest - especially those with LQT1. LCSD surgery is available in a few LQTS centers, providing another important treatment option for those