Clues or Miscues?
How to Make the Right Interpretation and Correctly Diagnose Long-QT Syndrome
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The congenital long-QT syndrome (LQTS) is an inherited condition associated with a prolongation of the QT interval on the ECG characterized by syncope, seizures, and sudden death secondary to ventricular arrhythmia, specifically torsade de pointes.1 LQTS is particularly notable because it affects seemingly healthy children and young adults, often with no apparent serious health issues. Unfortunately, LQTS may present dramatically with sudden cardiac death in 10% of children and syncope or seizures in 30% to 40% as the first symptom.2 Importantly, although LQTS has a high mortality when not diagnosed and treated, the currently available therapies are very effective in preventing sudden cardiac death.3 Thus, making the correct diagnosis in as many individuals with LQTS as possible before life-threatening symptoms emerge is critical.

Background of LQTS

The condition now designated as LQTS was first described as the Jervell Lange-Nielsen syndrome (LQTS with hearing deficit) in 1957.4 A few years later, the Romano Ward syndrome was described (LQTS with normal hearing).5,6 In 1979, the International LQTS Registry was established.

Much of the information about LQTS, correlations between genotype and phenotype, risk stratification, and treatment of LQTS stems from information gleaned from this registry and other large cohorts.7–11 Identification of the gene mutations in cardiac ion channels in the 1990s led to further understanding of LQTS. At least 9 genes have been identified that encode for proteins that modulate ion channel structure, function, and signaling or trafficking; alter cardiac repolarization; and increase the risk for ventricular arrhythmias.3,12 The identified genes are thought to represent 70% of the mutations that cause LQTS, with others yet to be identified or their location on identified genes yet to be found.

The authors13 of “Diagnostic Miscues in Congenital Long-QT Syndrome” in this issue of Circulation have illustrated many potential pitfalls in determining the accurate measurement of the QT interval and thus the accurate diagnosis of LQTS. They point out the hazards of incorrect diagnosis and treatment, including the use of medication, lifestyle modification, and implantable defibrillators in individuals who do not have this diagnosis, and appropriately illustrate the ECG findings that are commonly misread as prolongation of the QT interval, leading to a misdiagnosis. They label these “miscues.”

Although overdiagnosis can lead to serious issues for those individuals who are misdiagnosed with LQTS, a failure to suspect or diagnose LQTS can lead to a potentially irreparable outcome of sudden cardiac death. Thus, it may be helpful to clarify what is known about the diagnosis of LQTS and how the practicing physician can make the best decision for the individual patient.

Who Should Be Evaluated for LQTS?

Any patient who presents with syncope during or immediately after exercise or in association with physical or emotional stress or unexplained, atypical, sudden unexpected or frequent syncope or patients who present with ventricular tachycardia, especially torsade de pointes, or an aborted sudden cardiac arrest should have an ECG with corrected QT intervals measured. Family members of patients diagnosed with LQTS should be evaluated, starting with an ECG, with genetic testing when a family mutation is known. With the increased acquisition of ECGs in children for a variety of reasons, children with no known symptoms are being incidentally identified as having borderline or slightly long QT intervals, and the question of LQTS is being raised.

Review of Diagnostic Criteria: What Are the Clues?

The diagnosis of this syndrome is made from a variety of criteria or clues. These criteria involve measurement of the QT interval and a careful history for syncope, seizures, and arrhythmias in the patients or their families. A high level of suspicion is needed to diagnose these patients.

Schwartz et al14 provided criteria suggesting a scale for identifying these patients in 1985, with an update in 1993 involving measurement of the QT interval, review of the ECG, and a careful history for syncope, seizures, and arrhythmias in the patients and their families.

In the clear-cut cases, LQTS presents with a distinctly abnormal resting ECG showing a markedly prolonged QTc interval and abnormal T-wave morphology, syncope, possibly secondary to torsade de pointes, or an episode of aborted sudden cardiac arrest. The less dramatic patient with LQTS provides a challenging diagnostic dilemma. The resting ECG may not be abnormal (12% to 30% of LQTS patients),11,15 the

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patient may not have symptoms, and the family history may not be positive. In these patients, LQTS may be difficult to diagnose clinically. Genetic testing may be diagnostic and has become clinically available but often is expensive, is not covered by insurance, and remains difficult to obtain in a timely fashion. Most often, the clinical evaluation continues to be the mainstay of the initial diagnosis of LQTS.


When LQTS is suspected, an ECG should be obtained for the patient, and the QTc should be hand calculated and read by an individual familiar with LQTS and the measurement of the QT interval. Studies have shown wide variability in the measurement of the ECG, indicating that cardiologists or heart rhythm specialists may not agree or “accurately” measure the QT interval.16 Similarly, a manual calculation often differs from the computer-based measurement.

The best measurement of the QT interval is in leads II and V6. There is some agreement that the upper limit of normal is 0.46 seconds for individuals <15 years of age, 0.47 seconds for adult women, and 0.45 seconds for adult men.17 One must realize that a number of patients with genetic mutations for LQTS will have QTc intervals <0.44 seconds.11,15 Conversely, a significant portion of the normal population will have QTc intervals of 0.46 to 0.47 seconds. Very long QTc intervals, >0.50 to 0.53 seconds, are associated with increased episodes of sudden cardiac arrest.18,19

Although 6 types of correction of the QT interval for heart rate variations have been proposed, the Bazett formula is generally used. It is not linear, overcorrecting <60 bpm and undercorrecting at high rates. The presence of sinus arrhythmia makes the calculation of the QTc difficult unless it is clearly abnormal at all R-R intervals.

**Role of QTc Interval in LQTS Diagnosis**

The diagnosis of LQTS is easiest when the QTc is clearly prolonged but often cannot be made from a QT interval alone. A major dilemma in diagnosing LQTS is that the QT interval is not prolonged in all patients with LQTS and may be normal in 12% to 30% of the individuals who are gene positive.15 Reports from the Long QT Registry indicate that serial ECGs provide the greatest opportunity to make an accurate diagnosis.19

**More Detailed Evaluation of the ECG**

Patients with LQTS often have bizarre, flat, late-peaking, or notched T-wave morphology; alternating polarity (T-wave alternans); or prominent U waves or TU-wave complexes. It is the U wave that is a major concern in the Taggart et al study, providing an important opportunity to help the reader understand the true character of the long-QT ECG. Experts in the field have long known that a combination of factors on the ECG, not just the QTc interval, help to make the diagnosis. The various morphological variations of the T wave were well described by Moss et al,20 and correlations to various genotypes have further clarified these abnormalities. The presence of these factors alone, similar to the QTc interval measurement, does not make the diagnosis but adds to the pieces of the puzzle.

When the question of LQTS is raised in a child, an ECG should be obtained in both parents and other siblings. A striking abnormality in a parent or sibling may increase the index of suspicion in the child and target the best individual on whom to obtain genetic testing.

Additionally, the use of provocative testing, including exercise stress testing or epinephrine challenge, to uncover QTc interval prolongation, T-wave abnormalities, or ventricular arrhythmias has been suggested as a way to uncover LQTS.

**Clues in the History**

**Patient History/Symptoms and Clinical Associations**

The clinical associations are important clues. Patient should be asked if they have fainted or become dizzy with exercise or just after; if they have ever had syncope, palpitations, or rapid heart rates precipitated by exercise, fear, fright, startle, or strong emotions; or if they have been diagnosed or treated for a seizure disorder. Unexplained syncope with or immediately after exertion in children and young adults should be considered serious until proven otherwise. Up to 20% of patients who have LQTS and present with syncope, but are not diagnosed and treated, will have sudden cardiac death in the first year after the syncope, and 50% have sudden cardiac death by 5 years. Syncope in the past 2 years is a poor prognostic indicator in patients with LQTS.18

Syncope or cardiac events have been found to be associated with specific gene mutations. Clinical associations include exercise, especially swimming (LQT1); fear, fright, emotions, auditory stimuli, postpartum interval, and drugs (www.qtdrugs.org) (LQT2); or rest or sleep (LQT3 but also LQT2). Gender and age associations indicate that LQT1 patients are most likely to present before 9 years of age, especially boys, whereas LQT2 and LQT3 commonly present in the teenage years. LQT1 patients have more events, but the events in LQT3 are more likely to be fatal.3,20,21 The difficulty with all of these associations is the overlap that makes absolute genotype-phenotype associations challenging at this time.

**Family History**

A detailed family history can provide further clues to the correct diagnosis. One must inquire about both sides of the family. Questions about unexplained fainting or seizure disorders, deafness, sudden infant death syndrome, sudden unexpected deaths in young family members <30 to 50 years of age, and deaths by drowning or car accidents may uncover important information. One should not forget to ask specifically about the presence of LQTS. Questions should extend to parents, siblings, grandparents, and other relatives.

**Genetic Testing: Who Should Have Genetic Testing and What Does It Mean?**

Genetic testing is the gold standard for the diagnosis of LQTS but may not be readily available. It should be obtained in individuals with aborted sudden cardiac arrest and abnormal
QTc or T-wave abnormalities or sudden cardiac arrest with no known cause, in relatives of individuals identified with a LQTS mutation, and in other selected individuals in whom a diagnosis of LQTS is suspected. A negative test does not indicate that the individual does not have LQTS because 30% of the genes or location of the genetic mutations have not yet been identified. Although many polymorphisms are common, their exact role is unclear, with a potential for additive risk.

How the Puzzle Fits Together
The diagnosis of LQTS is made from a variety of criteria or clues. Knowing how to interpret each of these pieces of information, including the ECG, clinical associations, and family history, and fit them together is essential. A high index of suspicion does not equal overdiagnosis. In the absence of confirmatory (genetic) data or unequivocal clues—marked QTc prolongation, typical T-wave abnormalities, abrupt unexplained syncope (especially with exercise or emotion), typical ventricular arrhythmias (torsade de pointes), aborted sudden cardiac arrest, and a positive family history—the physician should continue to question and work to confirm the diagnosis.

The factors that Taggart et al suggest are most responsible for miscues in diagnosis, the QTc interval and the symptom of syncope, are exactly the same factors that are most important in making the correct clinical diagnosis of LQTS. Knowing the correct way to interpret the clue is the key to making the correct diagnosis.

Understanding the Impact of a Diagnosis of LQTS
There is no doubt that LQTS has an indelible impact on a family, especially when associated with a loss. They live in constant fear of an unthinkable event occurring. The individual, especially if a teenager, often is asked to give up activities from which he or she gains self-esteem and enjoyment. Although this diagnosis has the potential to be lifesaving, it clearly is a life-changing diagnosis and should not be taken lightly.

Balancing the Impact
It is important to work with patients’ families to balance the impact of this condition as much as possible, including working with schools and coaches to find activities that are safe but not so constrictive as to remove the patient from normal interactions with their peers. Not all activities need to be curtailed.

Diagnostic Changes
Even with the excellent points raised by Taggart et al and the information provided as to the correct ways to measure and identify abnormal QT intervals, the measurement of the QTc interval will continue to be challenging in many patients. The broad spectrum of “normal” T- and U-wave patterns in children and athletes needs to be clarified. The risks of asymptomatic patients with mildly prolonged QTc intervals or in those with gene mutations but normal QT intervals and no symptoms remain to be elucidated.

Although some patients may have received a mistaken diagnosis and unwarranted therapies, there definitely are cases in which it is difficult to make a diagnosis with certainty but that are very suspicious for LQTS. One might choose to give these patients a diagnosis of probable LQTS, start a β-blocker, obtain an automated external defibrillator for the home and school, and continue an ongoing evaluation, including additional clinical and genetic testing.

The important issue is to make the correct diagnosis, not whether it is worse to overdiagnose or underdiagnose LQTS. The problem is not too much awareness of the lethal impact of LQTS but too little awareness of the detailed process needed to make a correct diagnosis. More, not less, awareness is needed, combined with an educational effort regarding the best methods of clinical diagnosis. Additionally, a concerted effort must be made to convince insurance carriers that the genetic diagnosis is the gold standard for the 70% to 75% of patients who can have a gene identified. Making a correct diagnosis affects not only the patient but also the many family members who may carry the same gene mutation for LQTS. Failure to make the correct diagnosis can result in a sudden cardiac arrest or death in the individual initially being evaluated or in family members.

Disclosures
None.

References


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