Congenital Long QT Syndrome

Najeeb Ahmed, MD, Kamran Riaz, MD, FACC, Ripudeep Rai, MD, Mohammed Osman, MD, Abdul Wase, MD, FACP, FACC

Department of Internal Medicine, Wright State University Boonshoft School of Medicine, Section of Electrophysiology, Good Samaritan Hospital, Dayton, OH

Long QT syndrome (LQTS) can be asymptomatic—identifiable as an incidental finding on electrocardiogram—or it can present with palpitation, syncope, seizures, or sudden cardiac death. LQTS is characterized by a prolonged QT interval, which can be associated with a specific form of polymorphic ventricular tachycardia known as torsade de pointes. Other electrocardiogram changes in LQTS include T-wave abnormalities, particularly bifid T waves, U waves, and T-wave alternans. The precipitating factors of LQTS include electrolyte abnormalities, bradyarrhythmias, medications (such as antiarrhythmic drugs, antibiotics, antipsychotics, and antihistamines), and myocardial ischemia. The authors report a case of LQTS in a 47-year-old woman with no other significant cardiac history.

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The long QT syndrome (LQTS) is an inherited, autosomal genetic disorder associated with delayed cardiac repolarization and a prolonged QT interval on the electrocardiogram ECG. Clinically, it can lead to ventricular arrhythmias, torsade de pointes (TdP), and cardiac arrest. Patients generally present with sudden unexplained syncope, collapse, new onset of epileptic seizures, or sudden cardiac death. TdP may be the first manifestation of LQTS,

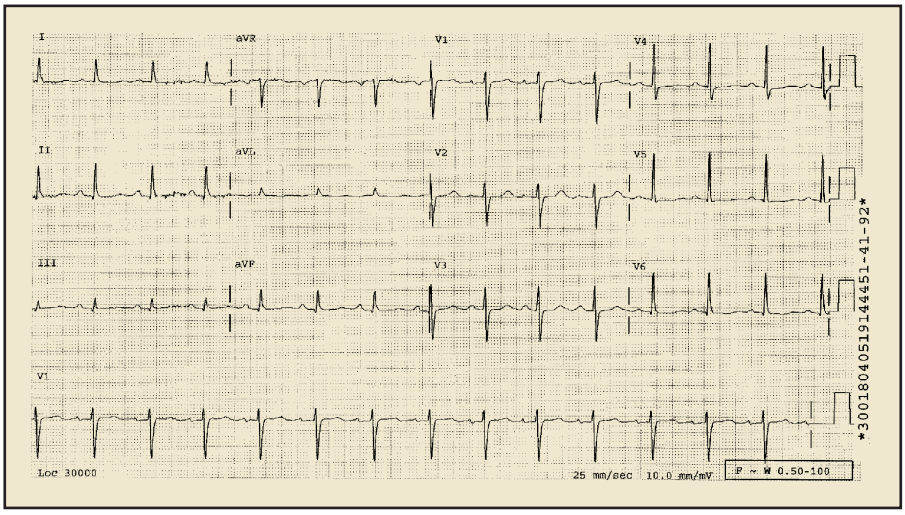


Figure 1. *Electrocardiogram showing normal sinus rhythm.*

occurring upon exposure to a torsadogenic drug. The authors report a case of LQTS in a 47-year-old woman with no other significant cardiac history.

Case Presentation

A 47-year-old woman with a history of bipolar disorder, chronic back pain, and asthma presented to the emergency room with nausea and vomiting. En route to the hospital, the patient had received 2 doses of phenergan 12.5 mg IV, and in the emergency room she received ondansetron 4 mg IV. She reported a long-standing history of palpitations, episodes of presyncope for the last 10 years, and at least 1 episode of syncope. She was a former smoker and regular marijuana user. There was no family history of sudden cardiac death, palpitations, near syncope, or syncope. Her medications included lorazepam 1 mg twice daily, sertraline 150 mg/d, gabapentin 600 mg in the morning and 800 mg at night, and oxycodone hydrochloride/acetaminophen and albuterol as needed.

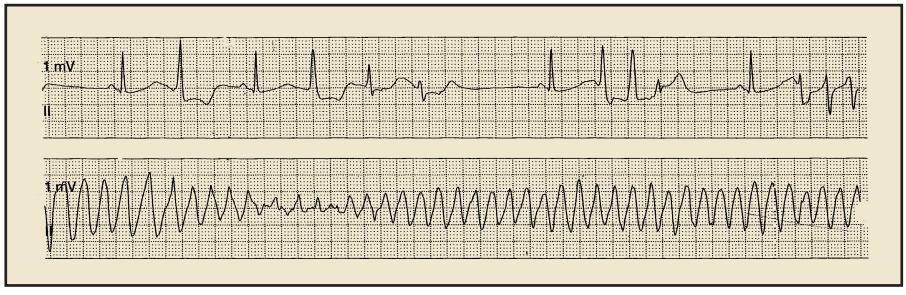
Physical examination revealed blood pressure of 128/63 mm Hg; pulse, 68 beats/min; temperature, 98.3°F; respiratory rate, 22 breaths/min; and oxygen saturation on room air, 100%. Other findings of the physical examination were unremarkable. Her complete blood count, blood chemistry, and cardiac markers were normal. A chest x-ray did not reveal any acute pathology. Her ECG on admission (Figure 1) revealed normal sinus rhythm, and the QTc interval was 453 milliseconds as calculated by computer.

While under observation in the emergency room (rhythm strip-lead II; Figure 2), the patient developed a syncopal episode; the monitor showed TdP, which rapidly degenerated into ventricular fibrillation. The patient was resuscitated and required defibrillation to restore sinus rhythm. She quickly regained consciousness and was transferred to the intensive care unit for further management; empiric IV magnesium supplementation was administered. An echocardiogram showed normal left ventricular function, with an ejection fraction of 55%. The patient also underwent cardiac catheterization, which revealed patent coronary arteries and normal left ventricular function. The following day, the patient underwent insertion of an implantable cardioverter defibrillator (ICD). Two days later, her QTc was normal (Figure 3). The patient had no further episodes of TdP during her hospitalization and was discharged in stable condition. Screening of her family members was advised.

Discussion

LQTS can be asymptomatic—identifiable as an incidental finding on ECG—or it can present with palpitation, syncope, seizures, or sudden cardiac death. This condition is characterized by a prolonged QT interval, which can be associated with a specific form of polymorphic ventricular tachycardia known as TdP. In this form of ventricular tachycardia, QRS complexes appear to be twisting around the isoelectric line, hence the name "twisting of the points."

Figure 2. *Electrocardiogram showing torsade de pointes.*



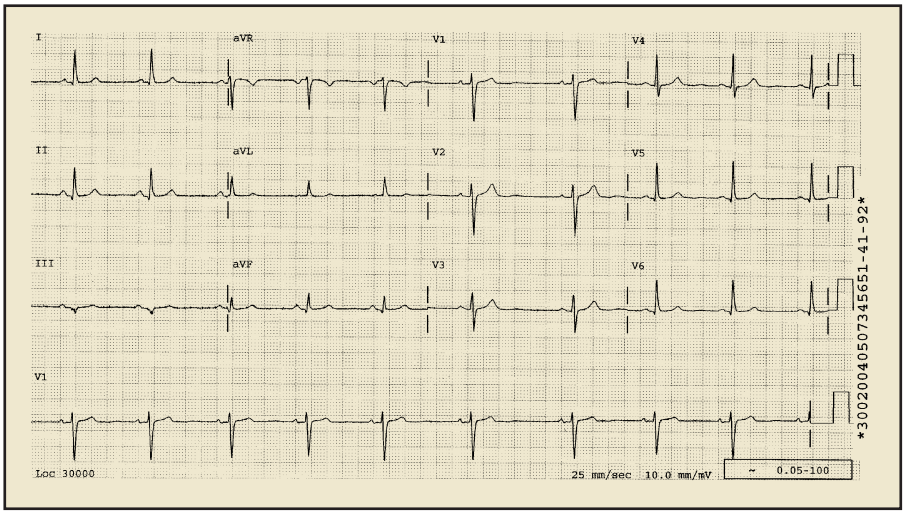


Figure 3. *Electrocardiogram showing a normal corrected QT interval.*

Generally, cases of LQTS can be designated as either congenital or acquired. However, some patients with acquired LQTS have a genetic predisposition that can be stimulated by a variety of precipitating factors. Table 1 lists precipitating causes of TdP among patients with LQTS.

Classically, congenital LQTS can present with 1 of 2 phenotypes: Romano-Ward syndrome, an autosomal dominant condition that can result from any mutation affecting genes responsible for LQTS; and Jervell and Lange-Nielsen syndrome, an autosomal recessive condition associated with sensorineural deafness.[1-3]

Jervell and Lange-Nielsen syndrome is a more severe form of LQTS, characterized by abnormalities in KCNQ1 (90% of patients), a gene responsible for coding the slowly activating delayed rectifier potassium current (I_{Ks}). In 50% of cases, patients present with symptoms before age 1, and the average QTc interval is >550 milliseconds. In about 10% of patients, the abnormal gene is KCNE1. Four factors have been identified that are associated with favorable prognosis for these patients: female gender, QTc <550 milliseconds, no history of syncope/cardiac arrest before age 1, and abnormalities in gene KCNE1.[4]

Mutations in 7 genes have been identified as causing LQTS: KCNQ1 (KVLQT1, LQT1), KCNH2 (HERG, LQT2), SCN5A (LQT3), ANKB (LQT4), KCNE1 (MinK, LQT5), KCNE2 (MiRP1, LQT6), and KCNJ2 (LQT7) (Table 2).[5-10] Defects in KVLQT1, HERG, and SCN5A probably account for $>90\%$ of identified cases of LQTS. Overall incidence is 1 in 7000 to 10,000. Several studies show a predominance of females. A similar female preponderance has been described in drug-induced TdP, supporting a link between the inherited and the drug-associated arrhythmias.

For LQT1 and LQT2, different triggers can precipitate the arrhythmia, including exercise; emotion; sudden awakening from sleep by an alarm clock, telephone, or thunder; and swimming or diving. Such triggers are probably associated with a sudden increase in sympathetic activity. However, for LQT3, cardiac events usually occur at rest or during sleep. Acquired LQTS is usually associated with electrolyte abnormalities or

Table 1
Precipitating Causes of Torsades de Pointes in Long QT Syndrome

1. Electrolyte abnormalities
   - a. Hypokalemia
   - b. Hypomagnesemia
   - c. Hypocalcemia
   - d. Anorexia nervosa
   - e. Liquid protein diet
2. Bradyarrhythmias
   - a. Sinus node dysfunction
   - b. Atrioventricular block
3. Medications
   - a. Antiarrhythmic drugs
     - i. Sotalol
     - ii. Dofetilide
     - iii. Quinidine
     - iv. Procainamide
     - v. Disopyramide
   - b. Antibiotics
     - i. Macrolides (eg, erythromycin)
     - ii. Fluoroquinolones (eg, levofloxacin, gatifloxacin)
     - iii. Pentamidine
   - c. Antipsychotics
     - i. Tricyclic antidepressants
     - ii. Haloperidol
     - iii. Risperidone
     - iv. Phenothiazines
     - v. Thioridazine
   - d. Antihistamines
     - i. Terfenadine
     - ii. Astemizole
   - e. Other drugs
     - i. Organophosphate insecticides
     - ii. Arsenic trioxide
     - iii. Cesium chloride
     - iv. Cocaine
     - v. Serotonin antagonists
4. Other causes
   - a. Myocardial ischemia
   - b. Human immunodeficiency virus infection
   - c. Intracranial disorders
   - d. Hypothermia
   - e. Connective tissue diseases with anti-Ro/SSA antibodies

Table 2
Genetics of Long QT Syndrome*

Genotype	Chromosome Locus	Gene Mutation
LQT1	11p15.6	KVLQT1†
LQT2	7q35-36	HERG†
LQT3	3p21-24	SCN5A†
LQT4	4q25-27	ANKB
LQT5	21q22.1-22.2	KCNE1
LQT6	21q22.1-22.2	KCNE2
LQT7	17q23	KCNJ2

*Currently identified LQTS disease genes with their chromosomal locus.
†Mutations in KVLQT1, HERG, and SCN5A probably account for > 90% of identified cases of long QT syndrome.

exposure to certain medications (see Table 1). A comprehensive list of medications that can precipitate LQTS is available at www.qtdrugs.org.

The ECG changes in LQTS include T-wave abnormalities, particularly bifid T waves and U waves, in addition to prolongation of the QT interval. The Bazett formula is still the common method of calculating the QTc interval:

QTc = measured QT/square root of RR interval in seconds

The average QTc interval in patients with LQTS is 490 milliseconds, with a range of 410 to > 650 milliseconds.[11] If QTc is < 410 milliseconds in men or < 430 milliseconds in women, LQTS is unlikely. During extremes of heart rate, the QTc interval may not be accurate. Similarly, during atrial fibrillation, an average of several QT intervals should be considered when calculating the corrected QTc interval. In some patients with congenital LQTS, an ECG may not necessarily show prolongation of the QT interval. An ECG performed before the index arrhythmia may show a completely normal QT interval.[12] Provocation with low-dose epinephrine (0.05 μg/min) may unmask the classic notching of the QT interval in certain subtypes, although the test has not yet reached the high sensitivity or specificity necessary to establish diagnosis or make therapeutic recommendations.[13] Recently, in LQT1, the QT stress test with low-dose epinephrine has shown that the QTc interval, paradoxically, is increased by 78 milliseconds. Thus, low-dose epinephrine can unmask LQT1 with a high degree of accuracy, with a positive predictive value of 76% and a negative predictive value of 96%.[14]

Typically, the onset of the arrhythmia is heralded by short-long-short RR intervals, which are usually caused by a premature ventricular contraction followed by a compensatory pause. It can also be associated with bradycardia or frequent pauses. Prolonged repolarization with consequent early after depolarization (EAD) and triggered activity is the proposed mechanism for LQTS. EAD occurs in phase 3 of monophasic action potential and corresponds to the U wave of the surface ECG. The amplitude of the EAD may reach the threshold for depolarization, thus triggering the polymorphic ventricular tachycardia characteristic of TdP. The taller the U wave, the higher the EAD, posing a greater risk of arrhythmia. Rarely, a patient may demonstrate visible T-wave alternans, which may herald a malignant arrhythmia.

Almost all drugs that cause LQTS block the outward rapidly activating delayed rectifier potassium current (I_{Kr}) that is mediated by the potassium channel encoded by the HERG gene;[5] the only exception is LQT3, in which the gene mutation is located on the Na channel. I_{Kr} is responsible for phase 3 depolarization. The degree of blockade by these drugs is inversely related to the extracellular potassium concentration and the heart rate.

The mortality among untreated symptomatic patients with LQTS exceeds 20% in the year after the first syncopal episode and approaches 50% within 10 years.[15,16] Proper diagnosis requires a careful history and physical examination. Patients should be asked specifically about the use of any medications that may prolong the QT interval. The presence of an electrolyte disorder and bradycardia with or without atrioventricular heart blocks should be ascertained. A scoring system has been developed for diagnostic purposes (Table 3).[17] Exercise ECGs and Holter monitoring may also be helpful.

In LQT2 and LQT3, β-blockers alone may not be sufficient.

The initial therapy of choice is administration of a β-blocker; however, a recent study reported a rate of events—defined as syncope, TdP, cardiac arrest, or sudden cardiac death—

Table 3
Point System for the Diagnosis of Congenital Long QT Syndrome (LQTS)

	Points*
Electrocardiogram Findings	
Corrected QT interval	
≥ 480 milliseconds	3
460-760 milliseconds	2
450 ms (men)	1
Torsade de pointes	2
T-wave alternans	1
Notched T wave in 3 leads	1
Low heart rate for age	0.5
Clinical History	
Syncope	
With stress	2
Without stress	1
Congenital deafness	0.5
Family History	
Family members with LQTS	1
Sudden death in family members age < 30 years without defined cause	0.5

*Scoring system: < 1 points, low probability; 2-3 points, intermediate probability; > 3.5 points, high probability. Adapted from Schwartz PJ.[17]

of 10% among patients with LQT1 genotypes, 23% among those with LQT2 genotypes, and 32% among those with LQT3 genotypes.[18] Therefore, in LQT2 and LQT3, β-blockers alone may not be sufficient. Other therapeutic options include left cardiac sympathetic ganglion denervation (cervicothoracic sympathectomy), cardiac pacing, and insertion of an ICD; the ICD offers pacing as well as defibrillation capabilities. For high-risk patients, a combination of β-blockers, left cardiac sympathetic ganglion denervation, and ICD may be indicated. Ongoing trials from the National Institutes of Health are investigating the role of gene-specific drugs such as sodium channel blockers in LQT3 syndrome and spironolactone in LQT2 syndrome. The ICD is used as first-line therapy when the presenting event is a resuscitated cardiac arrest.[19] Other pharmacologic interventions have also been proposed on the basis of experimental studies; these include alpha-blockers, calcium channel blockers, potassium channel openers, and sodium channel blockers.[15,19] A careful family history and genetic screening are advised for patients with newly diagnosed LQTS and their families. ■

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Main Points

- Long QT syndrome (LQTS) can be asymptomatic—identifiable as an incidental finding on electrocardiogram—or it can present with palpitation, syncope, seizures, or sudden cardiac death. This condition is characterized by a prolonged QT interval, which can be associated with a specific form of polymorphic ventricular tachycardia known as torsade de pointes.
- Congenital LQTS can present with 1 of 2 phenotypes: Romano-Ward syndrome, an autosomal dominant condition that can result from any mutation affecting genes responsible for LQTS; and Jervell and Lange-Nielsen syndrome, an autosomal recessive condition associated with sensorineural deafness. Defects in KVLQT1, HERG, and SCN5A probably account for >90% of identified cases of LQTS.
- Acquired LQTS is usually associated with electrolyte abnormalities or exposure to certain medications.
- The ECG changes in LQTS include T-wave abnormalities, particularly bifid T waves and U waves, in addition to prolongation of the QT interval. The average corrected QT interval in patients with LQTS is 490 milliseconds, with a range of 410 milliseconds to > 650 milliseconds.
- Therapeutic options include ß-blockers, left cardiac sympathetic ganglion denervation, cardiac pacing, and insertion of an implantable cardioverter defibrillator (ICD); the ICD offers pacing as well as defibrillation capabilities.

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