CLINICAL PRACTICE

Long-QT Syndrome

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

After the sudden death of a 13-year-old girl while she was playing basketball, her family comes to the clinic for medical evaluation (Fig. 1). Her parents' resting electrocardiograms (ECGs) are normal, but her 9-year-old sister's ECG shows an abnormally long QT interval. There is a history of recurrent syncope in female relatives of the maternal grandmother, but there is no family history of other sudden deaths, the sudden infant death syndrome, drowning, or death from a motor vehicle accident. How should these family members be further evaluated and treated?

THE CLINICAL PROBLEM

Sudden death in an otherwise healthy young person is an emotionally devastating event and unfortunately an all-too-common presentation of genetic arrhythmia syndromes. The most common of these syndromes is the long-QT syndrome, which is characterized by abnormal QT-interval prolongation on the surface ECG and an increased risk of sudden death, usually due to ventricular fibrillation. Physical stress and emotional stress are common triggers of syncope or sudden death in the long-QT syndrome; occasionally these events are triggered by loud noises or occur while the person is at rest.[1-3]

Hundreds of mutations in 10 genes linked to the long-QT syndrome have been identified (Table 1; and Table A in the Supplementary Appendix, available with the full text of this article at www.nejm.org).[9,10] Mutations in three genes, each encoding a cardiac ion channel that is important for ventricular repolarization, account for the vast majority of cases; the resulting genetic subtypes are called LQT1, LQT2, and LQT3 (Table 1). Most reported mutations are in coding regions, although noncoding mutations (resulting in the loss of allele expression) have also been described.[11-13] Most families with the condition have their own mutations, which are often termed "private" mutations; an emerging body of data suggests that the location of the altered amino acid (or acids) within the ion-channel proteins may affect the prognosis.[14,15] Some clinical features such as QT morphologic characteristics, the response of the QT interval to exercise, triggers of arrhythmia, and the response to therapies vary according to the disease-associated gene. Disease-associated genes (described in Table A in the Supplementary Appendix) are rare, and generalizations regarding gene-specific presentations or responses to therapy are therefore less reliable than those in common subtypes.

Syncope in patients with the long-QT syndrome is generally attributed to the form of polymorphic ventricular tachycardia called torsades de pointes. The LQT3 form of the syndrome can also be associated with bradycardia, and slow heart rates may cause syncope in some patients. Death is usually due to ventricular fibrillation. Most cases are associated with the autosomal dominant form of the syndrome (i.e., the Romano–Ward syndrome), with striking variability in clinical phenotypes

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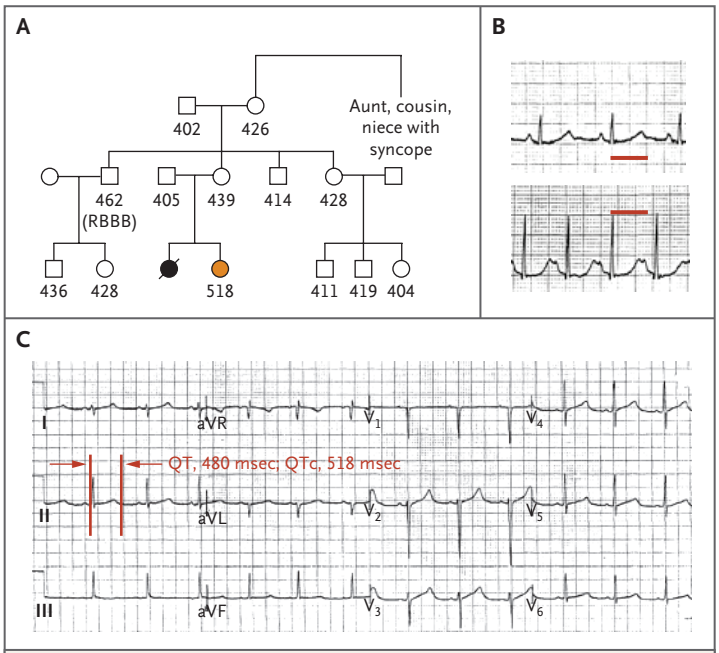

Figure 1. Family Tree and Electrocardiographic Findings of the Patient and Her Family.

In Panel A, the black circle denotes the 13-year-old girl who died playing basketball, and the orange circle denotes her sister. The numbers indicate QT intervals (in milliseconds) corrected for heart rate (QTc). The parents are both 39 years of age. The characteristics of the kindred have been modified to maintain anonymity. Panel B shows the lead II recordings in the proband's mother before (top) and after (bottom) exercise. The QT interval (indicated by the red lines) is identical before and after exercise, showing the "failure to shorten" that is typical of the LQT1 form of the disease. Panel C shows the electrocardiogram of the sister (represented by the orange circle in Panel A). The QT interval in lead II is shown. The proband's sister, mother, and maternal grandfather (who had a QTc of 402 msec in his mid-70s) were all LQT1 mutation carriers; this illustrates the variable penetrance in the long-QT syndrome. Syncope in the relatives on the maternal grandmother's side could not be attributed to the proband's mutation. RBBB denotes right bundle-branch block.

among mutation carriers; this is called variable penetrance.[16] Transmission is not strictly mendelian; an excess of mutation carriers — especially female mutation carriers — has been reported among the offspring of mutation carriers.[17] The risk of syncope and sudden death is decreased during pregnancy but increased in the postpartum period; the risk associated with the postpartum state appears to be increased among women with the LQT2 subtype as compared with women with the LQT1 or LQT3 subtype.[18]

This is a disease primarily of the young, and syncope and sudden death appear to be unusual in patients older than 40 years of age,[19,20] although data in such patients are limited. Moreover, only a minority of LQT1 mutation carriers have these events at a younger age, as compared with about half of LQT2 and LQT3 carriers.[20]

LQT1 is the most common form of the syndrome, and it arises from loss-of-function mutations in *KCNQ1*, which encodes I_{Ks}, an adrenergic-sensitive potassium current in the heart.[21] In this form of the disease, syncope or sudden death is triggered by emotional or physical stress; diving and swimming are LQT1-specific triggers.[4] QT-interval prolongation may be especially notable during or after exercise or epinephrine challenge.[22] In rare cases, patients inherit loss-of-function alleles in one of the genes encoding I_{Ks} from both parents, resulting in severe prolongation of the QT interval, a high risk of sudden death, and congenital deafness; these features are characteristic of the autosomal recessive Jervell and Lange-Nielsen syndrome (see Table A in the Supplementary Appendix).

LQT2 arises from loss-of-function mutations in *KCNH2* (also known as *HERG*), which encodes I_{Kr}, another important potassium current in the heart. Syncope or sudden death can occur with stress or at rest,[4] and the triggering of events by sudden loud noises, such as that produced by an alarm clock, is virtually diagnostic of this form[23]; hearing is normal.

LQT3 arises from mutations that disrupt fast inactivation of the cardiac sodium-channel *SCN5A*. As a result, the inward sodium current persists abnormally during the plateau of the cardiac action potential and prolongs the QT interval. *SCN5A* mutations that reduce the peak sodium current are also one cause of the Brugada syndrome. This syndrome, like the long-QT syndrome, is associated with a distinctive ECG finding (i.e., elevation of the right precordial ST segment), variable penetrance, and an increased risk of sudden death due to ventricular fibrillation.

The incidence of mutations is at least 1 per 2000 persons; this estimate is based on the results of genetic screening in families and the incidence of compound heterozygotes (i.e., persons with two mutations).[24,25] Since most mutation carriers remain asymptomatic throughout life,[9] clinical disease is less common.

The evaluation of the family of a young person who has died suddenly raises difficult questions. What is the precise diagnosis, and who in the extended family should be screened, and how?

Table 1. Common Forms of the Long-QT Syndrome.*

Variable	Genetic Subtype		
	LQT1	LQT2	LQT3
Disease-associated gene	*KCNQ1*	*KCNH2*	*SCN5A*
In vitro effect	Decreased I_{Ks}	Decreased I_{Kr}	Increased plateau I_{Na}
Setting of arrhythmia†	Emotional or physical stress, swimming, diving	Emotional or physical stress, sudden loud noise	Rest, sleep
Typical resting ECG‡	Broad T wave	Low-amplitude T wave with notching	Long isoelectric ST segment
ECG at onset of arrhythmia§	No pause	Pause	Not established
QT change with exercise	Failure to shorten	Normal	Supranormal
QT shortening with mexiletine¶	No	No	Yes
Clinical response to beta-blockers‖	Yes	Less than LQT1 response	Uncertain

* ECG denotes electrocardiogram, I_{Kr} the rapid component of the delayed rectifier current, I_{Ks} the slow component of the cardiac delayed rectifier current, and I_{Na} the cardiac sodium current.
† Data are from Schwartz et al.[4]
‡ These are typical patterns, but exceptions and variants are well recognized. Data are from Moss et al.[5]
§ Data are from Tan et al.[6]
¶ Data are from Schwartz et al.[7]
‖ Data are from Priori et al.[8]

How should mutation carriers be counseled and treated?

STRATEGIES AND EVIDENCE

DIAGNOSIS

Common presentations of the long-QT syndrome are palpitations, presyncope, syncope, and cardiac arrest. In addition, asymptomatic persons may be evaluated because the diagnosis is established or suspected in a family member. The differential diagnosis includes common causes of syncope in the young; these causes range from benign conditions such as vasovagal syncope to serious genetic conditions such as hypertrophic cardiomyopathy and catecholaminergic polymorphic ventricular tachycardia.[26-28] The history can help with the differential diagnosis and point toward specific subtypes of the long-QT syndrome. The physical examination and echocardiography (or magnetic resonance imaging, if performed) show no abnormalities in patients with this syndrome; thus, they are helpful only in ruling out other diagnoses.

An abnormal ECG obtained while the patient is at rest is the key to diagnosis. The QT interval, the surface ECG representation of ventricular repolarization, is affected by the patient's heart rate and sex; the upper limits of the QT interval corrected for the heart rate (the QTc) are below 460 msec for women and below 440 msec for men. Yet establishing a diagnosis of the long-QT syndrome may not be straightforward. Physicians may misread the QT interval[29] or misdiagnose vasovagal syncope as the long-QT syndrome.[26] In addition, mutation carriers may have normal ECGs, although this is unusual in patients with symptoms. The Schwartz scoring system, which includes ECG features and personal and family history, has been widely used,[30] but it does not take into account genetic information.[31] All persons with QT-interval prolongation should be screened for acquired causes such as hypocalcemia, hypothyroidism, and the use of drugs that can prolong the QT interval; these drugs include antiarrhythmic agents such as sotalol and dofetilide and noncardiovascular drugs such as haloperidol, methadone, and pentamidine. Most drugs that cause torsades de pointes block the rapid component of the delayed rectifier current (I_{Kr}), and previously unrecognized long-QT syndrome, of any subtype, can be identified in 5 to 20% of patients with drug-induced torsades de pointes.[32-34]

A detailed family history is essential. This evaluation should assess not only a history of sudden death, but also other deaths that may have been a manifestation of the long-QT syndrome, such as drowning, the sudden infant death syndrome,[35] and the death of a family member while he or she was driving (a potential manifestation of syncope).

Exercise testing can be useful to assess the

response of the QT interval (Fig. 1B and Table 1), but arrhythmias are very rare. The epinephrine challenge has been used to identify mutation carriers in families with the LQT1 mutation.[22,36] Holter monitoring and electrophysiological testing are generally not useful.

GENETIC TESTING

The long-QT syndrome is a clinical diagnosis, but genetic testing may provide additional information. Clinical features such as triggers of syncope and specific QT morphologic attributes[5,37] (Fig. 2) in patients in whom the clinical diagnosis has been made can suggest the affected gene in 70 to 90% of patients.[38,39] Genetic testing for the common subtypes of the long-QT syndrome is now available commercially, and it can identify a mutation in 50 to 75% of probands in whom the diagnosis appears to be certain on clinical grounds. The lack of detection in the remainder of the probands is probably due to technical difficulties with genotyping,[40] noncoding variants,[11-13] or as yet unidentified disease-associated genes. Thus, a negative genetic test does not rule out the diagnosis. There is also the potential for false positive results, since detection of a previously undescribed mutation does not establish the diagnosis. Rather, further analysis (e.g., linkage within a family or in vitro studies) may be required to establish the functional significance of any given variant; rare DNA variants of little functional consequence are well recognized.

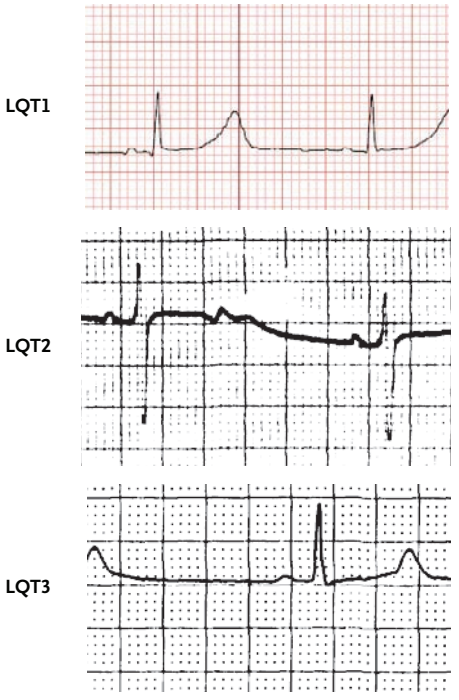

Figure 2. Electrocardiographic Patterns in the Three Common Forms of the Long-QT Syndrome.

The LQT1 form of the long-QT syndrome is associated with a broad T wave without a shortening of the QT interval due to exercise (as shown in Fig. 1C). LQT2 is associated with low-amplitude, often bifid, T waves. LQT3 is associated with a long isoelectric segment and a narrow-based, tall T wave. Although patterns may suggest a specific genotype of the long-QT syndrome,[5] many variants have been described.[37]

Genetic testing for the long-QT syndrome is most useful in two settings. First, when a clinical diagnosis is relatively certain, knowing the specific gene affected (or the site of the mutation within the gene)[14,15] may clarify the prognosis and guide therapeutic choices. Second, in a family with an affected proband and a known genetic defect, the genotyping of family members can help rule out the diagnosis in some persons. However, a positive test identifies a family member as being a mutation carrier, even if he or she is asymptomatic, has a normal QT interval, and is unlikely ever to have an event; this identification may have attendant consequences for long-term therapies and screening in his or her own family. A positive genetic test also could be used in a discriminatory fashion (e.g., to withdraw health insurance), although the pending Genetic Information Nondiscrimination Act is meant to remedy this situation. Detailed genetic counseling is warranted before proceeding to this testing, particularly for asymptomatic persons for whom the option of not testing must also be recognized.

Genetic testing has not been evaluated in patients who present with a borderline QT interval, suspicious symptoms (e.g., syncope), and no relevant family history. In these patients, the incidence of false positive and false negative results and their implications for management remain unknown.

RISK STRATIFICATION

The most powerful predictor of risk is the QTc duration.[20,41-43] In an analysis of 647 LQT1, LQT2, and LQT3 mutation carriers, the incidence of syncope or sudden death by 40 years of age in those with a QTc interval in the lowest quartile (<446 msec) was less than 20%, whereas it was

more than 70% among those in the highest quartile (>498 msec).[20] In the same study, features identifying patients at particularly high risk (>50% risk of an event before 40 years of age) included a QTc interval of more than 500 msec in carriers with LQT1 and LQT2 and male sex in carriers with LQT3; predictors of lower risk (<30% risk of an event before 40 years of age) included a QTc interval of less than 500 msec in carriers with LQT1 and male sex in carriers with LQT2. Although some of the subgroups were small and the effects of therapy were not controlled, these findings underscore the concept that risk is a continuum in this disease. Mutations that appear to be especially severe have been reported,[14,44] although the numbers of affected patients and families are small.

THERAPY

The lack of randomized trials of therapy in the long-QT syndrome reflects both the relative rarity of the disease and the heterogeneity in the type and severity of its clinical presentations. Data to guide management are generally from large registries and referral centers and thus are biased toward patients with severe disease.

Persons with a very low risk of sudden death (e.g., elderly mutation carriers with normal QT intervals) need not be treated, although even in these persons, it is prudent to avoid drugs known to prolong the QT interval. The major therapeutic options for the long-QT syndrome are beta-blockers and implantable cardioverter–defibrillators (ICDs).

The mainstay of therapy for the long-QT syndrome has been beta-blockade. Long-acting preparations such as nadolol and atenolol are usually used, and the efficacy of beta-blockade is assessed by blunting of the exercise heart rate (e.g., by >20%); beta-blockers do not substantially shorten the QT interval. Extensive observational data before[1-3] and after[42] the identification of disease-associated genes have shown superior survival among symptomatic patients who received beta-blockers (or occasionally among those who underwent left stellate ganglionectomy)[45] as compared with those who did not. Observational data have suggested that syncope or sudden death is less likely during beta-blocker therapy among patients with the LQT1 subtype (reported event rate among treated patients, 10% by 40 years of age) than among those with LQT2 or LQT3[8]; these findings are consistent with the adrenergic dependence of LQT1.

Sodium-channel blockers such as mexiletine and flecainide may normalize the QTc interval in patients with the LQT3 subtype,[46,47] but they may also increase the risk of sudden death in patients with overlapping Brugada syndrome[48,49]; their role as primary therapy in LQT3 thus remains uncertain. Identification of patients with both the LQT3 subtype and the Brugada syndrome may require further study (e.g., with the use of ECGs after monitored sodium-channel blocker challenge[48] or in vitro studies[49]).

The use of ICDs is widely considered in patients at high risk for sudden death, including those with symptoms before puberty, those with very long QTc intervals (e.g., >500 msec), and those with recurrent syncope thought to be due to arrhythmias, despite adherence to an adequate beta-blocking regimen. Some data also suggest that patients with cardiac arrest rather than syncope as the presenting symptom are at higher risk for sudden death.[50] Because of the adrenergic component triggering arrhythmias in the long-QT syndrome, the use of an ICD may be complicated by multiple shocks.[51]

AREAS OF UNCERTAINTY

The mechanisms underlying the variable penetrance of long-QT syndrome mutations are unknown. The elucidation of these mechanisms might facilitate risk stratification.

Because syncope or death in the long-QT syndrome is often adrenergically mediated, restriction of patients' participation in athletic activities is generally recommended. It is not known whether this restriction should extend to patients with forms of the disease in which adrenergic stressors are not prominent.

The appropriate role of ICDs remains controversial. Available data indicate that the severity of symptoms in the proband does not predict severity in affected family members.[41] A conservative approach is to reserve the use of ICDs for patients with symptoms that occur despite the use of beta-blocker therapy. A more aggressive approach is to implant an ICD in any affected person, including persons in whom the long-QT syndrome has been detected by means of family screening and in whom there is evidence of an increased risk of sudden death. An argument for

the liberal use of ICDs is their lifesaving potential in young, otherwise healthy patients. However, the associated costs and the observation that most patients who have mutations will never have cardiovascular events argue against this course.

Long-term follow-up studies involving patients receiving ICDs for primary prevention in this setting are needed to inform decision making. Further study may also identify genetic or sophisticated ECG markers that predict either increased or blunted risk in a mutation carrier, but it seems unlikely that any test will show that a carrier has no risk.

Finally, there is inevitably an intense wish on the part of families and physicians to avoid any risk after the death of a young mutation carrier. Thus, ICDs are likely to be used more as family screening becomes more common. ICDs are generally implanted in young patients who will have the device for decades. Advances that minimize even small risks associated with ICDs, such as component failure or infection, would be especially beneficial in younger patients.

GUIDELINES

The major cardiology and electrophysiology societies in the United States and Europe have jointly issued guidelines for the care of patients who are at risk for sudden death from cardiac causes. These patients include those with the long-QT syndrome (Table 2).[52]

CONCLUSIONS AND RECOMMENDATIONS

The evaluation of family members after the sudden death of a young person, as described in the vignette, should start with a detailed family history to elicit information about any other cases of sudden death, as well as deaths due to the sudden infant death syndrome, drowning, and motor vehicle accidents. Autopsy findings are usually normal in patients with fatal long-QT syndrome. If the proband has survived a cardiac arrest, imaging to rule out structural diseases is also normal. The key to diagnosis is the resting ECG; although a long QT interval suggests the syndrome, other causes of QT prolongation (e.g., hypocalcemia or hypothyroidism) should be ruled out. Occasionally, the diagnosis will become apparent only with provocation such as treadmill exercise or an epinephrine challenge. Families often come to clinical attention when a healthy young person has died, and grief counseling is integral to patient care in this setting.

Once the diagnosis of the long-QT syndrome has been established, further history, especially the circumstances surrounding the syncope or sudden death, and occasionally features of the ECG and genetic testing may assist in identifying

Table 2. Guidelines for Management of the Long-QT Syndrome.*

Recommendation	Level of Evidence†	Comment
No participation in competitive sports	I	Includes patients with the diagnosis established by means of genetic testing only
Beta-blockers	I	For patients who have QTc-interval prolongation (>460 msec in women and >440 msec in men)
	IIa	For patients with a normal QTc interval
Implantable cardioverter–defibrillator	I	For survivors of cardiac arrest
	IIa	For patients with syncope while receiving beta-blockers
	IIb	For primary prevention in patients with characteristics that suggest high risk; these include LQT2, LQT3, and QTc interval >500 msec‡

* Data are from the American College of Cardiology, the American Heart Association, and the European Society of Cardiology, in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Guidelines are adapted from Zipes et al.[52]

† Levels of evidence are as follows: I, conditions for which there is evidence or general agreement, or both, that a given procedure or treatment is beneficial, useful, and effective; II, conditions for which there is conflicting evidence or divergence of opinion, or both, about the usefulness and efficacy of a procedure or treatment; IIa, conditions for which the weight of evidence or opinion is in favor of usefulness and efficacy; and IIb, conditions for which the usefulness and efficacy are less well established by evidence or opinion.

‡ Other indicators of risk may include the specific site of mutation[14] and the postpartum period.[18]

a subtype. Genetic testing is also useful to establish or rule out the diagnosis in a family member of a patient with a known genetic mutation.

Beta-blockade with a long-acting agent is the mainstay of therapy. The use of an ICD should be considered, particularly when features suggesting an unusually high risk of sudden death are present; these features include especially long QT intervals, the onset of syncope with sudden noise or at rest, and certain ECG patterns (Fig. 2). In the family described in the vignette, beta-blockade is indicated in the 9-year-old sister and the mother (who is 39 years of age and carries the LQT1 mutation), but it would not be recommended for the maternal grandfather. The use of an ICD may be considered in the 9-year-old girl because she has one high-risk feature (QTc interval >500 msec), but this approach remains controversial, reflecting the challenges in managing this condition.

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