Congenital and Acquired Long QT Syndrome

Current Concepts and Management

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Abstract: Congenital long QT syndrome (LQTS) is a rare but potentially lethal disease, characterized by prolongation of QT interval, recurrent syncope, and sudden death. In the pregenomic era (1959–1991), sympathetic imbalance was thought to be responsible for this disease. Since 1991 (postgenomic era), 7 LQTS genes have been discovered and more than 300 mutations have been identified to account for approximately 70% of patients affected. Despite the advancement in molecular genetic knowledge, diagnosis of congenital LQTS is still based on electrocardiographic and clinical characteristics. Beta-blockers remain the mainstay treatment. For high-risk patients, the implantable cardioverter-defibrillator (ICD) offer an effective therapeutic option to reduce mortality. Gene-based specific therapy is still preliminary. Further studies are required to investigate new strategies for targeting the defective genes or mutant channels. For acquired LQTS, it is generally believed that the main issue is the blockade of the slow component of the delayed rectifier K^+ current (I_{Kr}). These I_{Kr} blockers have a "reverse frequency-dependent" effect on the QTc interval and increase the dispersion in repolarization. In the presence of risk factors such as female gender, slow heart rate, and hypokalemia, these I_{Kr} blockers have a high propensity to induce torsades de pointes. For patients with a history of drug-induced LQTS, care must be taken to avoid further exposure to QT-prolonging drugs or conditions. Molecular genetic analysis could be useful to unravel subclinical mutations or polymorphisms. Physicians not only need to be aware of the pharmacodynamic and pharmacokinetic interactions of various important drugs, but also need to update their knowledge.

Key Words: long QT syndrome, Romano Ward syndrome, Jervell and Lange-Nielsen syndrome, torsades de pointes, ionic channels

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Congenital LQTS is an inherited disease in children and adolescents who have a structurally normal heart but presented with sudden death in a high proportion of untreated patients. This uncommon disease was first described in 1957 in a family in which several children with QT prolongation, congenital bilateral neural deafness, and syncopal episodes died suddenly, with a family pattern suggesting autosomal-recessive inheritance (Jervell and Lange-Nielsen syndrome [J-LN]).[1] A similar but more common familial disorder with QT prolongation but without deafness was described in the early 1960s, with a family pattern of an autosomal-dominant inheritance (Romano-Ward syndrome [R-W]).[2,3] Congenital LQTS has been thought of as "idiopathic" for 3 decades, although "sympathetic imbalance" was considered to be a possible mechanism for the disease. The answers were finally disclosed in recent 10 years that the LQTS is an ion channel disease. Mutations causing the disease have been identified in 7 genes, accounting for more than 60% of patients who are affected.

EPIDEMIOLOGY

The precise incidence and prevalence of LQTS is unknown. For R-W syndrome, it is estimated to occur in 1 in 5000 to 10,000 individuals and is higher in certain areas, such as in Utah, U.S., and in Finland (1 in 5000).[4] J-LN syndrome is much rarer and the estimated prevalence is between 1.6 and 6 per million in children aged 4 to 15 years. LQTS causes 3000 to 4000 sudden deaths in children and young adults each year in the United States.[4] It is associated with a high mortality rate, which can be as high as 70% in untreated patients in 10 years.[5]

GENETICS AND MOLECULAR MECHANISMS

Genetic analysis of the R-W syndrome has so far identified 7 LQT genes in 6 chromosomes (Table 1).[6–13] They are named in the order of discovery. LQT1 (KCNQ1) was discovered by positional cloning technique. LQT2 (KCNH2) and LQT3 (SCN5A) were identified using the positional cloning-candidate gene approach. LQT4 (Ankyrin-B), LQT5 (KCNE1), LQT6 (KCNE2), and LQT7 (KCNJ2) were discovered by candidate gene approach. Currently, more than 300 mutations have been identified, and the list is still

TABLE 1. Genetics of Long QT Syndrome (LQTS)

LQTS Type	Gene	Chromosome Locus	Ion Channel	Effects	Percent of LQTS
Autosomal-dominant (Romano-Ward)					
LQT1 (1991)	KCNQ1 (KVLQT1)	11p15.5	α-subunit of I_{Ks}	$\downarrow I_{Ks}$	50%
LQT2 (1994)	KCNH2 (HERG)	7q35–36	α-subunit of I_{Kr}	$\downarrow I_{Kr}$	45%
LQT3 (1994)	SCN5A	3p21–24	α-subunit of I_{Na}	$\uparrow I_{Na}$	3–4%
LQT4 (1995)	Ankyrin-B	4q25–27		$\uparrow$ late I_{Na}?	<1%
LQT5 (1997)	KCNE1 (minK)	21q22.1–22.2	β-subunit of I_{Ks}	$\downarrow I_{Ks}$	<1%
LQT6 (1999)	KCNE2 (MiRP1)	21q22.1–22.2	β-subunit of I_{Kr}	$\downarrow I_{Kr}$	<1%
LQT7 (2001)	KCNJ2	17q23	$I_{Kir2.1}$	$\downarrow I_{Kir2.1}$	<1%
Autosomal-recessive (Jervell and Lange-Nielsen)					
JLN1 (1997)	KCNQ1 (KVLQT1)	11p15.5	α-subunit of I_{Ks}	$\downarrow I_{Ks}$	<1%
JLN2 (1997)	KCNE1 (minK)	21q22.1–22.2	β-subunit of I_{Ks}	$\downarrow I_{Ks}$	<1%

growing. Most (72%) mutations are missense mutations, leading to a single amino acid substitution. LQT1 and LQT2 are most commonly affected. Approximately 2% to 3% of patients carry 2 mutations. Patients with J-LN syndrome carry mutations (KCNQ1 or KCNE1) inherited from both parents.[14–16] These parents are usually asymptomatic. Most LQTS genes encode K^+ channels, with the exceptions of the LQT3 gene (SCN5A) that encodes the cardiac Na^+ channel, and LQT4 gene (Ankyrin-B) that encodes an adaptor protein that is involved in the anchoring of certain important proteins in the cell membrane.[13] Figure 1 shows the action potential of canine Purkinje fiber and the ionic channels involved in the congenital LQTS.

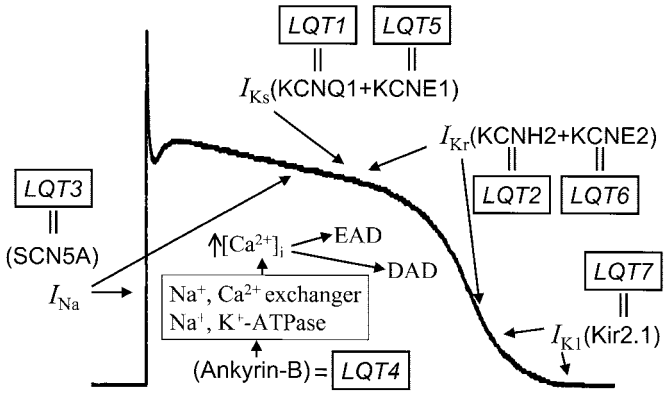

FIGURE 1. Action potential of canine Purkinje fiber. Seven LQTS genes and their responsible ionic currents were illustrated. EAD, early after depolarization; DAD, delayed after depolarization.

KCNQ1 and KCNE1 Coassemble to Form the Slow Component of the Delayed Rectifier K^+ Current (I_{Ks}) Channels

KCNQ1 (KVLQT1) encodes a channel protein with 6 transmembrane domains (S1-S6), a voltage sensor (S4), and a K^+-selective pore between S5 and S6, typical of a voltage-gated K^+ channel.[7] It forms the α-subunit of I_{Ks}. KCNE1 (minK) encodes a membrane protein that consists of 129 amino acids with a single putative transmembrane domain, but no K^+ channel pore signature sequence and no putative voltage-sensing domain. It forms the β-subunit of I_{Ks}. These 2 subunits coassemble to form I_{Ks} (Fig. 1).[17] At least 2 molecular mechanisms account for reduced channel functions in LQT1.[18] First, disease-associated intragenic deletions of 1 KCNQ1 allele result in syntheses of abnormal subunits that do not coassemble with normal subunits. This so-called "loss-of-function" mechanism results in a 50% reduction in the number of functional channels. Second, missense mutations produce channels with subtle structural abnormalities, but they can coassemble with normal subunits to form heterotetramers with varying stoichiometry. If 1 mutant subunit coassembles with 3 normal subunits in the channel tetramer, the resultant channel function could be depressed by more than 50% (dominant-negative effect), especially when the missense mutations occur in the pore region.[18] J-LN syndrome usually results from homozygous mutations in KCNQ1 or KCNE1 in consanguineous families. However, compound heterozygous mutations in KCNQ1 and KCNE1, with 1 mutant allele from the father and a different mutant allele from the mother, have been reported in J-LN syndrome.[16] Recently, recessive forms of R-W syndrome without deafness have been described in patients homozygous for KCNQ1 mutations.[19] Because these parents, like J-LN parents, are heterozygous for a

KCNQ1 mutation but have a normal QT interval, it is thought that not all KCNQ1 mutations are clinically manifest and that mild mutations in LQTS genes could be present among the general population and could predispose to drug-induced ventricular arrhythmias. These findings also provide the evidence that homozygous mutations in KVLQT1 do not invariably produce the J-LN syndrome. Both KCNQ1 and KCNE1 are expressed in the stria vascularis of the inner ears for maintenance of endolymph,[14] which is important in understanding the deafness seen in J-LN syndrome.

KCNH2 and KCNE2 Coassemble to Form the Rapid Component of the Delayed Rectifier K^+ Current (I_{Kr}) Channels

The LQT2 disease gene is KCNH2, also called *HERG* (the "human ether-a-go-go related" gene), which encodes a protein with 6 transmembrane segments (S1–S6), a voltage sensor (S4) and a K^+-selective pore between S5 and S6, typical of voltage-gated channel.[8] This is the α-subunit of I_{Kr}. Recently, a novel potassium channel gene (KCNE2) encoding *minK*-related peptide 1 (*MiRP1*) has been cloned.[11] It is located on chromosome 21, just 70 kb from KCNE1 (minK) gene. The 2 genes have significant homology at the DNA and amino acid level and likely resulted from a recent duplication. MiRP1 is the β-subunit of I_{Kr}, coassembling with KCNH2 to form I_{Kr} (Fig. 1). This outward current is the major contributor to the rapid repolarization of phase 3 of the action potential recorded from human myocytes. Like with KCNQ1, mutations of the gene cause loss-of-function or dominant-negative I_{Kr} suppression to decrease the repolarizing currents. Defects in biosynthetic processing or intracellular protein trafficking of mutant KCNH2 channel protein have also been reported. KCNE2 mutations have been implicated in drug-associated LQTS (see subsequently).[11] I_{Kr} is also the primary molecular target for methanesulfonanilide and most other blocking drugs known to cause torsade de pointes (TDP), thus linking the congenital and acquired syndromes. Furthermore, coexpression of KCNH2 with KCNE2 does appear to modulate drug sensitivity of I_{Kr}. KCNE2 mRNA expression is very low in ventricular muscle, but predominantly in Purkinje fibers in the canine heart,[20] suggesting an important role of mutations in KCNE2 in the excess prolongation of action potential in Purkinje fibers, leading to early after depolarizations (EADs) and TDPs. Homozygosity for a KCNH2 mutations could cause severe form of LQTS with marked QT prolongation, 2:1 atrioventricular block, and increased risk of sudden death but without deafness at birth.[21]

SCN5A Forms the α–Subunit of Human Cardiac Na^+ Channels

The gene responsible for LQT3 is SCN5A.[9] It encodes the α-subunit of the cardiac Na^+ channel with 4 homologous domains, each of which contains 6 transmembrane segments. Unlike the case with K^+ channels, expression of a single α-subunit of the cardiac Na^+ channel is sufficient to recapitulate I_{Na} (Fig. 1). Whereas the KCNQ1- and KCNH2-encoded gene defects represent a loss of channel function, the SCN5A-encoded defects generally result in a "gain of function" abnormality. Activation of these mutant Na^+ channels is normal and the rate of inactivation appears slightly faster than normal, but mutant channels can also reopen during the plateau phase of the action potential and prolong the action potential duration (APD).[22] Another recently reported mechanism was that a point mutation in the α-subunit of the human Na^+ channel induced a change in α- and β-interaction with resulting change in inactivation of the heteromeric channels.[23] The end result is a prolongation of cardiac action potential and an increased risk of TDP. Recently, homozygous SCN5A mutations with severe phenotype and 2:1 atrioventricular block have been reported, but there was no deafness in these patients.[24]

Ankyrin-B

The association of LQT4 with the targeting protein ankyrin-B stands in contrast to the other forms of LQTS.[13] Ankyrin-B's fundamental role is to recognize certain proteins such as Na^+/Ca^{2+} exchanger, Na^+ pump, and inositol-1,4,5-trisphosphate receptors, and to ensure that they are inserted into appropriate domains of cell membranes.[13] Two normal copies of the ankyrin-B gene are required for normal Ca^{2+} signaling, and missense mutation leads to loss-of-function. The loss of Na^+ pump function is probably the major contributor to elevated $[Ca^{2+}]_i$ transients in $AnkB^{+/-}$ ventricular myocytes, and causes delayed after depolarizations (DADs) and EADs.[13] However, there are several issues needed to be cleared up. Alterations in Ca^{2+} handling that generate arrhythmias do not generally delay repolarization, and actually the increase in QT interval observed in $AnkB^{+/-}$ mice is the result of delayed conduction. Yet, abnormalities in repolarization are clearly seen in LQT4 patients. In addition, the conduction slowing seen in ankyrin-B heterozygous mice cannot be attributed simply to Ca^{2+}-handling defects. Nevertheless, Ankyrin-B is the first identified protein to be implicated in a congenital LQTS that is not an ion channel or channel subunit.

KCNJ2 Forms $I_{Kir2.1}$ K^+ Channels

KCNJ2 is LQT7 gene.[12] It encodes $I_{Kir2.1}$, an important contributor to the inward rectifier K^+ current, I_{K1}. I_{K1} contributes no repolarization current during the plateau phase of the cardiac action potential, but provides substantial current during the late repolarization phase (Fig. 1). A reduction in I_{K1} prolongs the terminal phase of the cardiac action potential, and in the setting of reduced extracellular K^+, induced Na^+/Ca^{2+} exchanger-dependent DADs and spontaneous arrhythmias.[12] This is in contrast to what was observed in other

LQTS that reduced I_{Kr} and I_{Ks} or increased sustained I_{Na} prolonged the plateau phase of action potential. Thus, LQT7 shares some features of congenital LQTS such as QTc prolongation, but displays arrhythmias of syndromes associated with Ca^{2+} overload such as digitalis intoxication and catecholaminergic polymorphic ventricular tachycardia (VT).

Sympathetic Nervous System

Enhanced sympathetic activity can substantially increase spontaneous inward current through L-type Ca^{2+} channels to increase the likelihood of EAD. On the other hand, clinical data indicate that carriers of mutations in either KCNQ1 or KCNE1 are at increased risk of experiencing fatal arrhythmias in the case of elevated sympathetic activity. More recently, an adaptor protein, yotiao, was found to couple to the C-terminal of the KCNQ1/KCNE1 complex and bind to the regulatory enzymes protein: kinase A and protein phosphatase 1.[25] Therefore, this channel complex, through the adaptor protein, recruits enzymes that can upregulate and downregulate channel activity by phosphorylation (through protein kinase A) and dephosphorylation (through protein phosphatase 1) of a serine residue in its N-terminal domain.[25] When this complex molecular is disrupted, the channel is no longer regulated properly and there will be imbalance in the control of the action potential in the ventricle, leading to increased risk of arrhythmias.

Another link between the LQTS and the sympathetic nervous system is disclosed by a recent study showing that ERG genes are expressed in chromaffin cells, especially epinephrine-containing cells, and sustain a K^+ current.[26] Blockers of ERG channels modify the excitability of single chromaffin cell and increase the release of catecholamine. Thus, it is possible that LQT2 patients without β-blockers have a low heart rate and consequently their APD is particularly long before being awakened by the noise. At the time of sudden awakening, the chromaffin cells were greatly stimulated by the cholinergic input and secreted massive amount of epinephrine (not inhibited by ERG channel-sustained feedback) to reach the heart and prolonged the APD to the point of fibrillation and sudden death. If treated with β-blockers, such patients can survive.[26]

ELECTROPHYSIOLOGICAL MECHANISMS

The action potential in cardiac myocytes is distinctive in its duration (approximately 300 ms) in contrast to that from neurons and skeletal muscle (a few milliseconds). The long plateau phase is unique to ventricular and Purkinje fiber myocytes. In general, either the "loss-of-function" or the "gain-of-function" abnormality prolongs the APD, allowing for recovery from inactivation and reactivation of L-type Ca^{2+} channels (Ca^{2+} window currents), which triggers EADs from the plateau or early repolarization phase, mostly from Purkinje fiber myocytes or sometimes from midmyocardial cell (M cells). On the other hand, Ca^{2+}/calmodulin-dependent protein kinase II (CaM kinase) activity increased when APD was prolonged, and that in isolated hearts, EADs were blocked by CaM kinase inhibition, suggesting that CaM kinase plays a crucial link between increased APD- and EAD-related arrhythmias.[27] In human and canine hearts, M cells could constitute 30% to 40% of the myocytes in the left ventricular free wall, which have the longest APD as a result of smaller I_{Ks}, and a larger late I_{Na}. I_{Kr} density appears to be similar in all cell layers.

From an animal model of LQTS, it is realized that the initial beat of polymorphic ventricular tachycardia consistently arose as focal activity from a subendocardial site, whereas subsequent beats were the result of successive subendocardial focal activity, reentrant excitation, or a combination of both mechanisms.[28] The shift in QRS axis in TDP (twisting of the points) was the result of a predominantly single localized circuit that varied its location and orientation from beat to beat, with the majority of ventricular myocardium being activated in a centrifugal pattern. Thus, it is generally believed that the TDP is initiated from 1 or multiple foci but requires reentrant activity to sustain.

LQT3 carriers regularly present with bradycardia and sinus pauses. The mechanism has recently disclosed that 1 common mutation (1795 insD) in SCN5A causes a negative shift in inactivation of the persistent inward current and accounts for the bradycardia, whereas sinus pauses or arrest could result from failure of sinus node cells to repolarize under conditions of extra net inward current.[29]

ABNORMAL ELECTROCARDIOGRAM

Prolonged QTc Interval

The hallmark of patients with congenital LQTS is prolongation of QTc interval. A group of experts on LQTS recently proposed guidelines for measuring the QT interval.[30] They suggested that QT interval should be measured manually in 1 of the limb leads (usually lead II) from the beginning of the QRS complex to the end of the T wave and averaged over 3 to 5 beats. U waves should be included in the measurement if they are large enough to merge with the T wave. The QT interval should be adjusted for heart rate. Because the best way to adjust for heart rate has not been determined by prospective studies, a definite recommendation was not recommended.

Bazett correction formula ($QTc = QT \times RR^{1/2}$) is still the most widely used method for measuring QTc,[31] although it has been criticized for being inaccurate at fast heart rates ($>$90 beats/min). A QTc interval longer than 440 ms has been considered prolonged. However, data from the International Registry for LQTS showed that 68 (5%) of 1345 family members who have a QTc$<$440 ms had a cardiac arrest,[32] and only 70% of gene carriers have a prolonged QTc. The

others have reduced penetrance: 30% with a QTc ≤460 ms and 12% with a QTc ≤440 ms. However, none of affected gene carriers had a QTc of 410 ms or less, and no normal persons had a QTc of 470 ms or more (males) or 480 ms or more (females). Repeat electrocardiograms are necessary to identify disease carriers if the suspicion is high,[33] and a normal QTc and normal T-wave morphology does not exclude LQTS. The degree of the prolongation of QTc interval is not strictly correlated with the possibility of syncope attacks, although the occurrence of TDP is more frequent in patients with extremely prolonged QTc (>600 ms).

Measurement of QT is difficult when the patient is in atrial fibrillation because the QT interval varies from beat to beat depending on preceding R-R interval. In that case, the QTc intervals after the longest and the shortest R-R should be obtained and averaged. In addition, the QTc, and especially the T-wave morphology after the longer R-R interval, especially that follows the first sinus beat after termination of atrial fibrillation, should be carefully examined for the T-wave alternans and/or ventricular premature beat. In the setting of a wide QRS complex, it is accepted that a QTc more than 500 ms is considered prolonged.

In the normal population, females have longer QT intervals, probably as a result of QT shortening in males after puberty rather than QT prolongation in women during reproductive years.[33] In LQTS, men exhibit shorter mean QTc values than both women and children for both genotype-positive and -negative blood relatives. It is possible that adult gender differences in the propensity toward TDP reflect the relatively greater presence in men of a factor that blunts QT prolongation responses.

ST-T Morphology

Patients with LQTS could present with different patterns of ST-T morphologies. T-wave duration is particularly long in patients with LQT1. Patients with LQT2 usually have small T and/or notched T waves. T-wave onset is unusually prolonged in patients with LQT3. Recent investigation has expanded the findings to 10 typical ST-T patterns in LQTS (4 in LQT1, 4 in LQT2, and 2 in LQT3).[34] These different patterns, in combination with family-grouped analysis, were reported to be useful in prediction of genotype with a sensitivity of 83% to 85% and a specificity of 70% to 94%.[34] A notched T wave observed during the recovery phase of an exercise test is reported to be highly suggestive of LQTS. Beat-to-beat alternation of T-wave polarity or amplitude (T-wave alternans) could be observed briefly at rest but most commonly appears during emotional or physical stress and could herald TDP and is a marker for high-risk patients.

Torsades de Pointes

TDP starts with a premature ventricular depolarization, followed by a compensatory pause, and then a sinus beat with a markedly prolonged QT interval and an even more bizarre T wave (Fig. 2). This is then followed by a train of polymorphic ventricular tachycardia (TDP), whereas the first beat represents triggering from an EAD. The "short–long–short" sequence heralding TDP is a hallmark of both congenital and also acquired LQTS, although patients with congenital LQTS sometimes might not have this specific sequence before the onset of TDP. It is unknown why TDP reverts spontaneous to sinus rhythm in most instances but degenerates to ventricular fibrillation in others.

Other Electrocardiogram Abnormalities

QT dispersion in 12-lead electrocardiograms (ECG; Qtmax–QTmin, Qtcmax–QTcmin) is increased in LQTS patients compared with control subjects. Some reports suggest that the average resting heart rate is lower in LQTS patients, especially in children, compared with normal control subjects. In addition, patients with LQTS have a mean heart rate lower than normal control during moderate and maximal exercise. Sinus node dysfunction has been reported in patients with LQTS.

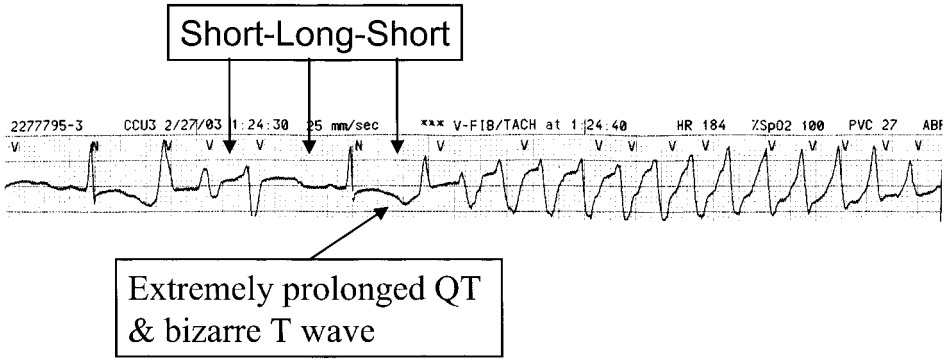

FIGURE 2. Torsades de pointes in a LQT1 patient with hypokalemia. The signature "short–long–short" sequence was shown leading to torsades de pointes.

SYMPTOMS

The feeling of palpitation or "fluttering" is uncommon because the TDP arrhythmia is usually too fast to support any circulation or any perceptible cardiac contractions. Otherwise, syncope, seizure-like activity, and cardiac arrest are the common clinical presentations. Neurally mediated syncope and epileptic seizures are the most common differential diagnosis. For symptomatic patients, approximately 50% suffered from the first cardiac event by the age of 12 and approximately 90% by the age of 40. Approximately 30% of carriers never have any symptoms.

Most data on clinical presentations were gathered before it was understood that multiple mutations, on multiple genes, could cause LQTS, and that patients could display highly variable phenotypes, including even no phenotype. Approximately 75% of all patients (almost all LQT1/LQT5 and 50% of LQT2/LQT6) have events precipitated by adrenergic stimuli. Patients with LQT1 seem to have a high frequency of cardiac events associated with vigorous physical activities, especially diving and swimming. Patients with LQT2 are particularly sensitive to arousal-type emotions such as sudden loud noise by ringing of an alarm clock or telephone. LQT3 patients experience events without emotional arousal during sleep or at rest. A higher incidence of syncope was found to occur during menstruation and in the postpartum period. In men, the risk for the first cardiac event is higher in childhood and decreases after puberty. In LQT1 (the most common), the risk of cardiac events is higher in males until puberty and higher in females during adulthood.[35] Atrial arrhythmias are not common in patients with congenital LQTS, although polymorphic atrial tachycardia have recently been reported in a group of LQTS patients.[36]

Except for QTc prolongation, the phenotype for LQT7 (Andersen syndrome) is different from those of other LQTS.[12] It is characterized by periodic paralysis and other physical features, including low-set ears, micrognathia, and clinodactyly. Thus, it is unique among ion channelopathies as a result of the combination of both a skeletal and a cardiac muscle phenotype. The mean QTc of male and female probands with LQT7 was 479 and 493 ms, respectively, compared with 497 and 510 ms for males and females with other forms of LQTS. Furthermore, although ventricular arrhythmias are common in patients with LQT7 (64%), sudden cardiac death was not reported.

DIAGNOSIS

Clinical suspicion is of pivotal importance in the diagnosis of LQTS. A typical presentation is that a child or young adult experienced an unexplained syncope or sudden death during physical exertion or emotional agitation, or suffered from a history of unexplained drowning or near-drowning.[33] Despite advances in the understanding of the molecular mechanisms underlying the cellular electrophysiological defects found in patients with LQTS, the diagnosis is still based on clinical characteristics of the patient and the family.

Widely used diagnostic criteria are shown in Table 2.[37] They are based on findings from the ECG, clinical history, and family history. In patients with intermediate probability, serial ECGs should be obtained, because the QTc value in patients with LQTS could vary from time to time. Furthermore, screening ECGs from other family members will be needed. Molecular genetic testing is useful in borderline cases and in family members of patients with LQTS. It seems appropriate to perform molecular screening in all family members of genotyped patients. Otherwise, the molecular genetic testing remains primarily a research tool and is not available for routine screening. Furthermore, it is successful in only 60% to 70% of clinically affected patients. Epinephrine has been used to unmask the latent mutation carriers with LQT1, but the overlap between the mutant gene carrier and the normal control is large.[38] Exercise testing, Holter monitoring, and invasive electrophysiological study are not very useful for diagnosis or risk

TABLE 2. Diagnostic Criteria in Long QT Syndrome (LQTS)[37]

	Points
Electrocardiographic findings*	
QTc†	
>480 ms	3
460–470 ms	2
450 (male) ms	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 definite LQTS¶	1
Unexplained sudden cardiac death	0.5
Before age 30 among immediate family members	

Scoring: <1 point = low probability; 2–3 points = intermediate probability >4 points = high probability.

Modified from reference 37 with permission.

*In the absence of medications or disorders known to affect these electrocardiographic features.

†QTc calculated by Bazett's formula, where $QTc = QT \times RR^{1/2}$.

‡Mutually exclusive.

§Resting heart rate below the second percentile for age.

‖The same family member cannot be counted twice.

¶Definite LQTS is defined by an LQT score >4.

stratification, but Holter recording of notched T waves enhanced detection of patients with LQT2.[39]

RISK STRATIFICATION

The severity profile of LQTS in a proband was not found to be useful in identifying the clinical severity of LQTS in affected first-degree relatives of the proband. A recent study of 647 patients from 193 consecutively genotyped families with LQTS showed that the risk of first cardiac event (syncope, cardiac arrest, and sudden death) before the age of 40 years and before therapy can be stratified by genotype, sex, and the length of the QT interval (Table 3).[40] These data provide a rationale for the treatment of asymptomatic patients. It is suggested that prophylactic treatment is warranted in intermediate- and high-risk patients: male and female patients with a mutation at the LQT1 locus who have a QTc of 500 ms or more, male patients with a mutation at the LQT2 locus who have a QTc of 500 ms or more, all female patients with a mutation at the LQT2 locus irrespective of the QTc, and all patients with a mutation at the LQT3 locus.[40] For patients with low risk, the treatment strategy should be individualized. It is also becoming clear that not only the gene, but also the region within a given gene in which a mutation occurs might have an impact on clinical outcome. Defects in the carboxy terminal of KCNQ1 are often benign, whereas pore region mutations of KCNH2 are associated with higher risk.[41]

TREATMENT

There is no disagreement that symptomatic patients need treatment. In untreated symptomatic LQTS patients, mortality rates exceed 20% in the year after the first syncopal attack, and the averaged annual risk of syncope is 5%. The overall mortality in 10 years is 50%. Beta-blockers, cardiac pacing, left cardiac sympathetic denervation (LCSD), and the implantable cardioverter defibrillator (ICD) markedly improve survival and reduce the 5-year mortality to 3% to 5%.

TABLE 3. Probability of a First Cardiac Event (Syncope, Cardiac Arrest, or Sudden Death)

Genotype	QTc	Sex	Risk
LQT1	≥500 ms	Male and female	High
	<500 ms	Male and female	Low
LQT2	≥500 ms	Male and female	High
	<500 ms	Female	Intermediate
		Male	Low
LQT3	≥500 ms	Male	High
		Female	Intermediate
	<500 ms	Male and female	Intermediate

Low risk: <30%; intermediate: 30–49%; high: ≥50%.
Data from reference[40].

For asymptomatic patients, there are differing opinions with regard to the need for treatment. Some investigators suggested that all asymptomatic LQT patients in the risk age (up to 40 years or so) should be treated, most with prophylactic β-blockers, because sudden death could be the first symptom. Schwartz et al.[42] recommended treatment of patients without symptoms in 6 conditions: 1) in all patients with J-LN syndrome, because the risk of cardiac events is particularly high; 2) in neonates and infants, because the risk is especially high during the first months of life; 3) in affected siblings of children who have died suddenly because of the emotional stress present in the family; 4) in patients with documented T-wave alternans, because this is a sign of enhanced electrical instability; 5) in patients with a very long QTc (>600 ms), a group thought to be more symptomatic; and 6) when there is anxiety and an explicit request for treatment in a family after thorough explanation. In a recent analysis done by Priori et al., prophylactic therapy was suggested for patients with intermediate and high risk of syncope, cardiac arrest, or sudden death.[40]

Beta-Blockers

Because 75% of the cardiac events are precipitated by adrenergic stimuli, beta-blockers remain the mainstay of therapy. Beta-blocker therapy decreases mortality from 71% in historical controls to 6% in a treated group. Syncope or other events recur in patients on beta-blockers in approximately 25% of cases, and the chance of sudden death at 5 years has been estimated to be 10% despite therapy. A recent study found unacceptably high mortality among high-risk groups treated with beta-blockers.[43] Patients who were symptomatic before beta-blocker therapy had a 32% risk of recurrent syncope or sudden cardiac death within 5 years on beta-blockers. Patients with a history of aborted cardiac arrest before starting beta-blockers had a hazard ratio of 12.9 for aborted cardiac arrest or death while on prescribed beta-blockers compared with asymptomatic patients.

Maximal beta-blockade is suggested. This can be assessed by a maximal heart rate less than 130 beats/min. No prospective comparative studies of the efficacy of various beta-blockers have been performed, but it seems appropriate to avoid those with intrinsic sympathomimetic activity. Propranolol is widely used at a daily dose of 2 to 3 mg/kg. Nadolol with a daily dose of 1 mg/kg is also widely used because of its longer half-life, particularly useful for young patients in whom missing dose is frequent. Noncompliance exposes patients to their baseline risk of cardiac events and probably accounts for a percentage of treatment failure, especially in adolescents. In patients who develop severe bradycardia or profound sinus arrest (eg, >2.0 sec), concomitant pacemaker therapy is indicated.

The precise mechanism of the efficacy of beta-blockers in LQTS remains unknown. The QTc remains prolonged after

effective treatment with beta-blockers, but QTc dispersion is decreased in the responders.[44] The persistence of excessive QT dispersion after therapy with β-blockers is 1 possible marker that could allow the early identification of patients likely to remain at high risk and could therefore suggest the need to proceed to alternate therapies such as LCSD.

Cardiac Pacing

Cardiac pacing is an adjuvant therapy to beta-blocker therapy in patients with bradycardia, atrioventricular block, or in patients with LQT3. LQT3 patients could derive particular benefit from pacing because the dispersion of repolarization worsens steeply during bradycardia in this genotype. However, concluding that other genotypes will not benefit from pacing is premature. The cardiac pacing should include a high lower rate limit (≥80 beats/min) and pause-prevention algorithm.

Left Cardiac Sympathetic Denervation

For patients who are resistant to beta-blockers, LCSD has been used as an alternative. There has been no randomized, controlled clinical trial to systematically evaluate the therapeutic efficacy of LCSD. The largest series enrolling 123 patients who were unresponsive to or did not tolerate the full dose of beta-blockers has demonstrated a marked decrease in the number of patients with cardiac events (from 99% to 45%) and in the number of cardiac events per patient (from 21 ± 31 to 1 ± 3) in 10 years.[42] Most of the patients who still had cardiac events after surgery had only 1 episode and usually during the first 6 months. The total incidence of sudden death was 8% in 10 years, and the 5-year survival rate was 94%. Thoracoscopic sympathectomy technique is the 1 with a short operative time and minimal complication. In humans, LCSD normalize the prolonged QTc, reduces the QTc dispersion, and thereby decreases the probability of cardiac event.

ICD

In a recent retrospective analysis of patients in the International Long QT Registry, patients who received ICD have a total mortality of 1.3% over 3 years compared with 14% in the non-ICD patients over 8 years.[45] Thus, ICD is suggested to be used in high-risk patients who were symptomatic before beta-blocker therapy or in patients in whom the combination of beta-blockers, LCSD, and/or pacing fails to prevent the syncopal attacks. It is also proposed as first-line therapy when the presenting event is a resuscitated cardiac arrest. On the other hand, ICD can produce emotional distress, which can trigger arrhythmias and shocks. To avoid shocks for episodes of short, self-terminating TDP, a revised detection and treatment algorithm has been incorporated into some devices.

Triggers from the Purkinje system or the right ventricular outflow tract have a crucial role in initiating ventricular fibrillation associated with the LQTS. More recently, these foci can be eliminated by focal radiofrequency ablation, but the long-term efficacy remains to be determined.[46]

Gene-Based Specific Therapy

Although molecular genetic studies raise the possibility of genotype-specific therapies targeting ion channels, there has not any long-term follow-up data yet. This therapy can only be viewed as adjuvant therapy at this moment. Nicorandil, an opener of the ATP-sensitive K^+ channel, has been shown to improve the repolarization abnormalities during epinephrine infusion in LQT1 patients and seems to be more effective in abbreviating the QT interval, reducing the transmural dispersion, and preventing TDP in LQT1 and LQT2 than in LQT3.[47] R-L3, a benzodiazepine, is the first and the only I_{Ks} activator to date. It shortened APD and suppressed EADs in ventricular myocytes. Most KCNQ1 mutant channels responded to R-L3 similarly to wild-type channels. R-L3 has the potential to provide gene-specific therapy for LQT1.[48]

For patients with LQT2, supplement of K^+ and spironolactone has been tried with optimistic results. The QTc was shortened, and QT dispersion and T-wave morphology were improved. Whether this will reduce the incidence of life-threatening events has not been tested in a long-term study.[49]

In LQT3 patients, experimental and clinical studies have suggested that the Na^+ channel blockers such as mexiletine, lidocaine, and flecainide could prevent the repetitive opening of the channel, shorten the QT interval, and normalize the morphology of the T wave.[50] The long-term effect needs to be determined.

Lifestyle Modification

For patients with LQT1, strenuous or competitive exercise, especially swimming and diving, should be avoided. Patients with LQT2 should be advised to remove sources of loud noise in their environment (such as alarm clocks and telephones). The cellular phone had better be switched to vibration mode. Dietary supplement of potassium might be needed in case of diarrhea or vomiting. For patients with LQTS in general, they should have a disease identification card in their pocket at all times. They should be alert enough to consult their doctor before taking any medication.

ACQUIRED LONG QT SYNDROME

Incidence

It is difficult to estimate the incidence of acquired LQTS. Although the chances of provoking TDP by a noncardiac medication are generally lower than antiarrhythmic medications, a number of noncardiovascular drugs have been recently withdrawn from the U.S. market because of unexpected postmarketing reports of sudden cardiac death associated with prolongation of QT interval and TDP. For example, terfenadine was withdrawn in 1998, astemizole and grepafloxacin in 1999, and cisapride in 2000.

Etiology and Pathophysiology

Table 4 shows lists of drugs that potentially cause TDP. The hallmark mechanism of drug-induced LQTS and TDP is the blockade of I_{Kr}, a major repolarization current in the heart. There are 2 important structural characteristics that account for the unusual susceptibility of I_{Kr} channels to block by various drugs. First, the inner cavity of the I_{Kr} channel appears to be much larger than any other voltage-gated K^+ channels. Thus, it can accommodate and trap large drug molecules.[51] Second, the S6 domains of I_{Kr} channels, but not other voltage-gated K^+ channels, have 2 aromatic residues that face into the inner cavity[52] that could bind large aromatic drugs by a π-stacking interaction.[53] In addition, the binding affinity of drugs is enhanced by inactivation of the I_{Kr}. Drugs that exclusively block I_{Kr} but have no effects on other ionic channels have especially higher propensity to induce TDP for the following reasons. They prolong the APD more in M cells and Purkinje fibers than in other myocytes because the former

TABLE 4. Potential of Drugs to Cause Torsades de Pointes by Expert Opinion

Drugs With Risk of TDP*	Drugs With Possible Risk of TDP†	Drugs to Be Avoided by Congenital LQTS (also include A and B)‡	Drugs Unlikely to Cause TDP§
Amiodarone	Alfuzosin	Albuterol	Amitriptyline
Arsenic trioxide	Amantadine	Atomoxetine	Amoxapine
Bepridil	Azithromycin	Cocaine	Ampicillin
Chlorpromazine	Chloral hydrate	Dobutamine	Ciprofloxacin
Cisapride	Dolasetron	Dopamine	Clomipramine
Clarithromycin	Felbamate	Ephedrine	Desipramine
Disopyramide	Flecainide	Epinephrine	Doxepin
Dofetilide	Foscarnet	Fenfluramine	Fluconazole
Domperidone	Fosphenytoin	Isoproterenol	Fluoxetine
Droperidol	Gatifloxacin	Levalbuterol	Galantamine
Erythromycin	Granisetron	Metaproterenol	Imipramine
Halofantrine	Indapamide	Midodrine	Itraconazole
Haloperidol	Isradipine	Norepinephrine	Ketoconazole
Ibutilide	Levofloxacin	Phentermine	Mexiletine
Levomethadyl	Lithium	Phenylephrine	Nortriptyline
Mesoridazine	Moexipril/HCTZ	Phenylpropanolamine	Paroxetine
Methadone	Moxifloxacin	Pseudoephedrine	Protriptyline
Pentamidine	Nicardipine	Ritodrine	Sertraline
Pimozide	Octreotide	Sibutramine	Trimethoprim–sulfamethoxazole
Procainamide	Ondansetron	Terbutaline	Trimipramine
Quinidine	Quetiapine		
Sotalol	Risperidone		
Sparfloxacin	Salmeterol		
Thioridazine	Tacrolimus		
	Tamoxifen		
	Telithromycin		
	Tizanidine		
	Vardenafil		
	Venlafaxine		
	Voriconazole		
	Ziprasidone		

Adapted from Website of The University of Health Sciences Center (http://www.qtdrugs.org/) with permission.
*Drugs that are generally accepted by authorities to have a risk of causing torsades de pointes.
†Drugs that in some reports could be associated with torsades de pointes but at this time lack substantial evidence for causing torsades de pointes.
‡Drugs to be avoided for use in patients with diagnosed or suspected congenital long QT syndrome. (Drugs on first 2 lists are also included here.)
§Drugs that, in some reports, have been weakly associated with torsades de pointes but that, when used in usual dosages, are unlikely to be a risk for torsades de pointes.

have lower I_{Ks} and higher I_{Na}, resulting in an increase of QT dispersion. They usually demonstrate "reverse frequency-dependent" effect; the degree of prolongation in APD is more prominent during slow heart rate, when the QT is already longer, than that during fast heart rate. The QT-prolonging capability is reduced during myocardial ischemia, in which interstitial hyperkalemia and increased circulating catecholamines limit their effects.

Amiodarone prolongs APD and QTc significantly, but the risk of TDP is much lower than quinidine or sotalol. It has been shown that amiodarone decreases both the transmural and the regional dispersion in the heart, suppressed EADs by its blocking effect on $I_{Ca,L}$ and I_{Na}, and does not have the "reverse frequency-dependent" effect. However, in general, the risk of developing TDP correlates with the degree of prolongation of QTc interval as shown in the following equation[54]:

$$\text{Risk} = 1.052^{X}$$

where X is a 10-ms increase in QTc interval. Thus, the risk of TDP in a patient with a QTc of 600 ms is almost triple that in a patient with a QTc of 400 ms.

The degree of prolongation of QTc interval usually correlates with the serum level of the drug. Thus, pharmacodynamic (both drugs block I_{Kr}) and pharmacokinetic (1 drug interferes with the clearance of another) interactions of a variety of drugs should be carefully examined. To avoid the former, it would be better to avoid prescribing more than 1 QT-prolonging drug unless it is deemed necessary and frequent monitoring of QTc is mandatory. To avoid the latter, we need to update our knowledge of drug metabolism. Cytochrome P450 (CYP450) 3A is responsible for the metabolism of the largest number of drugs followed by CYP2D6.

Table 5 shows the substrates, inhibitors, and inducers of these 2 isoenzymes. Both Tables 4 and 5 are expanding, and it would be hard for clinicians to memorize all the details. It is suggested that we check the information online (http://www.qtdrugs.org/; http://www.longqt.org/; http://www.torsades.org/; or http://www.fda.gov/medwatch/) or consult pharmacists whenever in doubt.

Concentration-dependent effect on the prolongation of QTc interval holds true for most drugs. Quinidine is a famous exception, in which TDP is well recognized to occur at "subtherapeutic" plasma concentrations. It now seems likely that this reflects the multiple electrophysiological effects of quinidine. At low concentrations, the drug is a potent I_{Kr} blocker, whereas at higher concentrations, the drug's actions to block inward current through Na^+ channels could actually reduce the risk of TDP.

Genetic Component of Acquired Long QT Syndrome

Phenotypically mild (subclinical) mutations or polymorphisms in LQTS genes could be present among the general population, and it has been suggested that these patients could be predisposed to drug-induced or hypokalemia-induced arrhythmias.[11,55,56] "Repolarization reserve" has been proposed that there is excess capacity of the myocardium to effect orderly and rapid repolarization through normal mechanisms. Potassium channel dysfunction attributable to subclinical mutations or polymorphisms could potentially be compensated by other K^+ currents, and normal repolarization was maintained. However, When QT-prolonging drugs were administered or during other conditions favoring QT prolongation such as bradycardia or hypokalemia, the "repolarization reserve" was exhausted, leading to QT prolongation and TDP. Therefore, molecular genetic analysis might be extended to those with acquired LQTS and their family.

Risk Factors

The risk or precipitating factors for TDP include existing long QT interval, history of acquired LQTS or TDP, hypokalemia, hypomagnesemia, hypocalcemia, slow ventricular rate, female gender, recent conversion from atrial fibrillation, rapid intravenous infusion rate, increased adrenergic tone immediately before TDP, conditions favoring increased intracellular calcium such as congestive heart failure and left ventricular hypertrophy, and myocardial ischemia. In patients with reduced "repolarization reserve," the presence of these risk factors could have cumulative effects in prolonging the QTc and lead to TDP. However, there is no way clinically to accurately predict or calculate the individual's "repolarization reserve." The presence of existing QT prolongation or a history of acquired LQTS or TDP might be used as possible surrogates to predict "repolarization reserve."

Treatment

The management of TDP was summarized in Figure 3. When polymorphic VT is encountered, the first step is to examine the QTc interval immediately before or after the tachycardia to see if it is prolonged. The treatment policy will be completely different according to the QTc measured (Fig. 3). When sinus rhythm is regained, efforts might be made to look for the possibility of congenital LQTS. Patients with congenital and acquired LQTS should keep away from any QT-prolonging drug or condition.

SUMMARY

Congenital LQTS is an inherited disease in children and adolescents who have structurally normal heart but presented

TABLE 5. Drug Metabolism by Cytochrome P450 3A and 2D6

CYP3A Substrates	Inhibitors	Inducers
Antiarrhythmics	Most HIV protease inhibitors	Barbiturates
Amiodarone	Most macrolides (not azithromycin)	Carbamazepine
Quinidine	Most azole antifungal drugs	Glucocorticoids
Lidocaine	Ketoconazole	Modafinil
Macrolides	Itraconazole	Phenobartital
Erythromycin	Fluconazole	Phenytoin
Clarithromycin (not azithromycin)	Miscellaneous	Rifampin
Nonsedating antihistamines	Amiodarone	Ritonavir
Astemizole	Cimetidine	Troglitazone
Terfenadine	Ranitidine	Pioglitazone
Prokinetics	Ciprofloxacin	
Cisapride	Norfloxacin	
Mosapride	Mibefradil	
Most HIV protease inhibitors	Diltiazem	
Most calcium channel blockers	Verapamil	
Most HMG-CoA-reductase inhibitors (not Pravastatin)	Fluvoxamine	
Most benzodiazepines	Nefazodone	
Miscellaneous	Norfluoxetine	
Cocaine	Grapefruit juice	
Cyclosporine		
Haloperidol		
Methadone		
Pimozide		
Tamoxifen		

CYP2D6 Substrates	Inhibitors	Inducers
Antipsychotics	Amiodarone	Dexamethasone
Haloperidol	Celecoxib	Rifampin
Risperidone	Chlorpromazine	
Thioridazine	Chlorpheniramine	
Chlorpromazine	Cimetidine	
Many tricyclic antidepressants	Cocaine	
Most IC antiarrhythmic drugs	Doxorubicin	
Many beta-blockers	Fluoxetine	
Miscellaneous	Metoclopramide	
Lidocaine	Methadone	
Mexiletine	Mibefradil	
Tamoxifen	Paroxetine	
Codeine	Quinidine	
Fluoxetine	Ranitidine	

with sudden death in a high proportion of untreated patients. More than 300 mutations have been identified in 7 LQT genes. Diagnosis still depends on ECG, clinical presentations, and family history. Molecular genetic testing is useful to unravel borderline family members of LQT probands. Beta-blockers remain the mainstay of treatment. ICDs are highly effective in reducing sudden cardiac death for high-risk patients. Gene-based specific therapy is still preliminary. Further studies are required to investigate new strategies for targeting at the defective genes or mutant channels.

The main cause of acquired LQTS is inhibition of I_{Kr}. For these patients, care must be taken to avoid further exposure to QT-prolonging drugs or conditions. Molecular genetic analysis could be useful to unravel subclinical congenital LQTS patients with reduced "repolarization reserve."

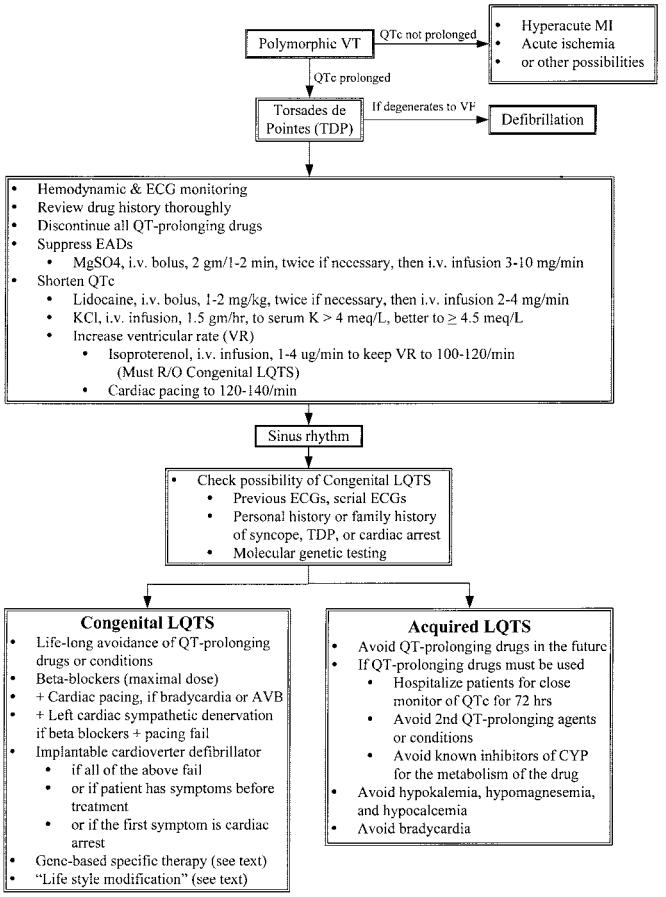

FIGURE 3. The algorithm for the acute management of torsades de pointes and long-term strategies for patients with congenital and acquired LQTS. AVB, atrioventricular block; CYP, cytochrome P450; EAD, early after depolarization; LQTS, long QT syndrome; MI, myocardial infarction; QTc, corrected QT interval; TDP, torsades de pointes; VR, ventricular rate; VT, ventricular tachycardia.

Physicians need to be aware of the pharmacodynamic and pharmacokinetic interactions of various important drugs.

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