REVIEW ARTICLE

Long QT Syndrome

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CME

To assess a physician's expertise on the basis of whether the doctor checks a patient's QT interval would be excessive, but the fact remains that in many cases, checking it saves lives. The author of a respected textbook on electrocardiography[1] wrote, "The measurement of the QT interval has little usefulness" in 1957 — the same year in which Jervell and Lange-Nielsen published their first report on the association between QT-interval prolongation and sudden death in a family with congenital deafness,[2] which was soon followed by similar findings reported by Romano and colleagues[3] and by Ward[4] in patients with normal hearing. In 1975, Romano–Ward syndrome and Jervell–Lange-Nielsen syndrome were grouped under the name long QT syndrome.[5]

Long QT syndrome is an uncommon disease of genetic origin with a documented prevalence of 1 in 2000 live births[6]; however, the actual prevalence is probably higher because the original prospective study, which involved 44,000 infants,[6] did not include genotype-positive–phenotype-negative persons. The syndrome is characterized by prolongation of the QT interval on an electrocardiogram (ECG) obtained when the patient was at rest and by a propensity for life-threatening arrhythmias that occur mostly under conditions of physical or emotional stress.[5,7] The clinical importance of the timely diagnosis of the syndrome stems from the fact that sudden cardiac death is often the first symptom, which makes remedying diagnostic or therapeutic errors impossible. As stated 50 years ago,[5] given the high efficacy of current therapies, the existence of patients with undiagnosed — and therefore untreated — long QT syndrome is nowadays inexcusable; unfortunately, missed diagnosis is still too often the case.

Genetic Basis of Long QT Syndrome

The three major genes associated with long QT syndrome (present in approximately 90% of cases), *KCNQ1*, *KCNH2*, and *SCN5A*, were identified in 1995 and 1996.[8-10] Variants in *KCNQ1* and *KCNH2* are the cause of long QT syndrome type 1 and type 2 in approximately 50% and 40% of patients with the syndrome, respectively; these genes encode the potassium channels conducting the outward currents I_{Ks} and I_{Kr}. These channels are critically important for cardiac repolarization, and the reduction in the I_{Ks} and I_{Kr} currents caused by pathogenic variants prolongs the QT interval and causes long QT syndrome.[11] During adrenergic activation, such as during physical activity, the I_{Ks} current becomes the prevalent repolarization current, and this alteration carries major clinical implications — if the QT interval does not appropriately shorten when the heart rate increases, ventricular fibrillation may ensue. The third major gene, *SCN5A*, encodes the voltage-gated sodium channel conducting the major depolarizing inward sodium current I_{Na}. Pathogenic variants of *SCN5A* producing gain of function prolong repolarization and cause long QT syndrome type 3 in approximately 10% of cases. Homozygous or compound heterozygous pathogenic variants in *KCNQ1*[12] and *KCNE1*[13] (encoding subunits of the potassium channel I_{Ks})

KEY POINTS

LONG QT SYNDROME

- Long QT syndrome is a leading cause of sudden death in young persons, with a prevalence exceeding 1 in 2000.
- It is characterized by prolongation of the QT interval, aberrant T-wave morphologic features, and the propensity toward life-threatening arrhythmias triggered mostly by adrenergic activation.
- Long QT syndrome is caused by variants in genes encoding primarily for potassium-ion and sodium-ion channels. Common genetic variants (in modifier genes) increase or decrease the arrhythmic risk linked to the disease-causing variants and can contribute to risk stratification.
- The current therapies — including treatment with beta-blockers, left cardiac sympathetic denervation, and mexiletine — are extremely effective and limit the need for an implantable cardioverter–defibrillator to a small percentage of patients. Genotype-specific management is important. Gene therapy is promising but is not yet ready for clinical use.
- Arrhythmic risk and the approach to therapy need to be reassessed at yearly visits to allow optimization of therapy.

cause the recessive Jervell–Lange-Nielsen syndrome associated with congenital deafness.[2,14]

Additional genes have been linked to long QT syndrome, but only a few play important roles.[15] Variants in the calcium-channel gene *CACNA1C* cause the Timothy Syndrome, which is a form of long QT syndrome and includes skeletal and neurodevelopmental abnormalities.[16] Variants of *CALM 1*, *CALM 2*, and *CALM 3*, encoding calmodulin, which modulates key cardiac ion channels,[17] cause calmodulinopathies (consequences of variants in calmodulin genes associated with life-threatening arrhythmias and other cardiac and noncardiac pathologic features).[18,19] The calmodulin genes are unique in that they are on different chromosomes and encode the same protein. Pathogenic variants in these three genes cause long QT syndrome by impairing calcium-channel inactivation,[17] thereby prolonging the QT interval.

Not infrequently, genetic reports in long QT syndrome identify variants of uncertain clinical significance, which can be puzzling for the managing physician. Such variants are periodically reclassified because increasing knowledge, usually derived from either robustness of the clinical phenotype,[20,21] evidence of familial cosegregation, or functional evaluation,[22] allows them to be reclassified to benign, probably-benign, pathogenic, or probably-pathogenic status,[23] often with implications for management. Despite long QT syndrome being primarily a monogenic condition, the contribution of common genetic variants in aggregate (represented by polygenic risk scores) could modulate patients' susceptibility to the syndrome, especially in patients who are genotype-negative.[24,25]

MODIFIER GENES

A large South African founder population[26] in which there was a wide spectrum of the QT interval corrected for heart rate (QTc) among hundreds of carriers of the same variant, *KCNQ1*–A341V, offered a unique opportunity to identify and study modifier genes in long QT syndrome.[27] The term modifier genes describes genetic factors, usually common, capable of modifying in either direction the consequences of disease-causing variants.[27] During the past 20 years, several modifiers have been identified,[27-29] with two main implications. On one hand, these modifiers allow a refinement of risk stratification to favor a more- or less-aggressive therapy. On the other hand, the cellular mechanism of action shown by modifier genes in long QT syndrome[27,29,30] paves the way for the design of new therapies targeting a specific molecular pathway.

CLINICAL PRESENTATION AND DIAGNOSIS

The key features of long QT syndrome are related to the ECG and to arrhythmic events. The QT interval is usually markedly prolonged and is often accompanied by bizarre morphologic changes with regard to ventricular repolarization (e.g., biphasic and notched T waves) that should arouse diagnostic suspicion even before measurements are taken; indeed, when dealing with long QT syndrome, pattern recognition is extremely important (Fig. 1 and Table 1). The upper limits of the normal values of the QTc (with correction for heart rate according to Bazett's formula[31]) are 440 msec and 460 msec for men and women, respectively.

Despite limitations, correction according to Bazett's formula usefully discriminates between normal and abnormal values, even in infants.[32] The QT interval should be measured from the Q wave to the return to baseline of the T wave: the tangent method, largely used because it saves time, often underestimates the actual length of ventricular repolarization, whereas the longest QT interval is the most important value to consider when assessing arrhythmic risk.[33] A QTc greater than 500 msec helps in discriminating between patients who are at moderate or high arrhythmic risk.[34] Notches on the T wave (Fig. 1), often accompanied by mechanical alterations,[35-37] are a marker of arrhythmic risk[38] owing to early afterdepolarizations, and are particularly frequent in patients with long QT syndrome type 2. T-wave alternans (Fig. 1), experimentally reproduced together with QT prolongation by stimulation of the left stellate ganglion in cats,[39] is an important prefibrillatory sign and a marker of major cardiac electrical instability. The T-wave morphologic features may help predict the specific genotype but cannot substitute for actual genetic screening.

The arrhythmic events are due to torsades de pointes ventricular tachycardia, which often degenerates into ventricular fibrillation, causing cardiac arrest and sudden death. The symptoms and outcome depend on the duration of torsades de pointes. In subjects with QT prolongation, the occurrence of short-duration syncope or vertigo should alert the physician to the possibility of torsades de pointes, often a harbinger of life-threatening arrhythmic episodes.

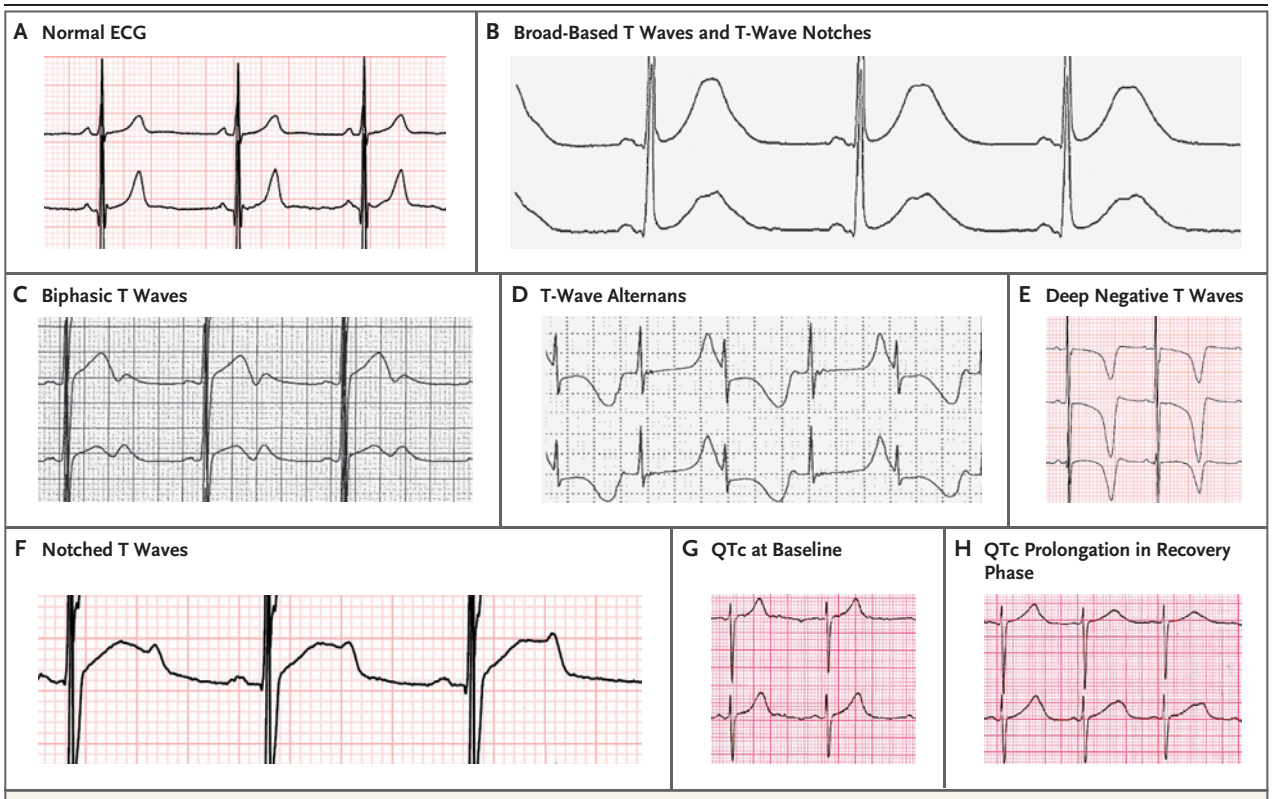

Figure 1. ECG Patterns Suggestive of Long QT Syndrome.

Some electrocardiographic (ECG) patterns are suggestive of long QT syndrome independent of the actual length of the QT interval. Panel A shows a normal ECG and a QT interval corrected for heart rate (QTc) of 417 msec. Panel B shows broad-based T waves and T-wave notches and a QTc of 615 msec. Panel C shows biphasic T waves and a QTc of 577 msec. Panel D shows T-wave alternans, a typical ECG feature of long QT syndrome and a marker of high electrical instability and a QTc of 776 msec. Panel E shows deep negative T waves and a QTc of 673 msec. Panel F shows notched T waves, typical of long QT syndrome type 2, with a QTc of 483 msec. Panel G and Panel H are from the same patient and show QTc prolongation in the recovery phase at the end of an exercise stress test with a QTc of 640 msec (Panel H) as compared with the baseline (Panel G) QTc of 472 msec. The QTc was measured by using the point of return to the baseline of the T wave, and an approximate 10-msec measurement error should be taken into account.

Table 1. Diagnostic Criteria for LQTS, 1993–2011.*

Criteria	Points†
Electrocardiographic results‡	
QTc§	
≥480 msec	3
460 to 479 msec	2
450 to 459 msec, in male patients	1
QTc ≥480 msec at 4 min of recovery from exercise stress test§	1
Torsades de pointes¶	2
T-wave alternans	1
Notched T wave in three leads	1
Low heart rate for age‖	0.5
Clinical history	
Syncope¶	
With stress	2
Without stress	1
Congenital deafness	0.5
Family history**	
≥1 Family member with confirmed LQTS	1
Unexplained sudden cardiac death in immediate family member younger than 30 years of age	0.5

* Modified from Schwartz et al.[49] with permission. LQTS denotes long QT syndrome.
† Total points indicate the probability of LQTS as follows: 0 to 1 point, low probability; 1.5 to 3 points, intermediate probability; 3.5 points or more, high probability.
‡ Electrocardiographic data shown were from patients who were not receiving medications and who did not have conditions that prolong the QT interval.
§ QT interval corrected for heart rate (QTc) is calculated according to Bazett's formula.[27]
¶ Torsades de pointes and syncope are mutually exclusive.
‖ Low heart rate for age is defined as a resting heart rate that is below the 2nd percentile for age.
** The same family member cannot be counted twice.

Gene-specific triggers for arrhythmic events in long QT syndrome have been identified.[40] Persons with long QT syndrome type 1 are at increased risk whenever sympathetic activity increases, as during emotional or physical stresses, especially swimming.[40] Persons with long QT syndrome type 2 are at increased risk when exposed to sudden noises, especially if they are at rest or asleep and are woken abruptly[40]; they are also exquisitely sensitive to low plasma potassium levels and to QT-interval–prolonging drugs, and female patients are at high risk during the postpartum period, probably owing to sleep disruption causing rebounds of the arrhythmogenic rapid-eye-movement sleep. Persons with long QT syndrome type 3 are at risk primarily at rest or when asleep (Table 2). Independent of genotype, infants with a cardiac event in the first year of life are at very high risk for death and are seldom protected by traditional therapies.[41] Long QT syndrome contributes to sudden death in infancy.[42] Up to 10% of infants who die suddenly in the first year of life[43] or in utero[44] carry long QT syndrome–causing variants, and in newborns a prolonged QTc increases the risk for sudden death.[45] Without genetic testing, the sudden death of an infant in the first months of life would be labeled as sudden infant death syndrome. This overly simplistic approach strengthens the rationale for widespread ECG screening in the first month of life,[46] with the objective of identifying infants with long QT syndrome who are at risk for death in the first year of life or later.[46] These considerations also call for restraint before assuming that sudden deaths in infancy among multiple siblings imply infanticide.[47]

In typical cases, such as syncope associated with clear QTc prolongation, diagnosis should be straightforward. In borderline cases (e.g., modest QTc prolongation and no symptoms) genetic screening may help, as well as the use of a 12-lead, 24-hour Holter recording, which often unmasks typical changes, especially at night. Prolongation of the QTc in the recovery phase of an exercise stress test or the appearance of a complete fusion of the T and P waves at peak exercise[48] can contribute to the diagnosis. Not every medical doctor is expected to diagnose long QT syndrome with certainty; however, when confronted with a child or teenager with a QT interval prolongation, with or without fainting episodes, once secondary causes are excluded, the syndrome should be suspected and the patient referred to a center with specific expertise. For doctors without specific experience in diagnosing long QT syndrome, a diagnostic score has been developed over the years and represents a useful tool for use in a preliminary assessment of the probability of the syndrome (Table 1).[49]

A number of tests have been suggested to facilitate the diagnosis of long QT syndrome in ambiguous cases.[50] The exercise stress test is the only one that is truly useful, because a marked QT prolongation at the 4th minute of recovery is highly specific for long QT syndrome.[49,51] The

Table 2. Genotype-Specific Management.*

Aspect of Management	LQT1	LQT2	LQT3
Response†			
Beta-blockers	+++	++	++
Left cardiac sympathetic denervation	+++	++	++
Mexiletine	Unknown	++	+++
Triggers or associated events	Adrenergic — strenuous exercise, swimming, and strong emotion	Startle (e.g., sudden, loud noises; alarm clock; telephone ringing), low serum potassium level, in postpartum period	Sleep or rest
Recommendations	Limit strenuous exercise (swimming allowed with supervision by an adult who can swim), avoid verbal or physical confrontations, yearly visit for risk reassessment	Preserve serum potassium level at ≥4 mmol per liter; avoid use of alarm clocks and telephone in the bedroom; beta-blockers taken morning and evening; in postpartum period, share bedroom to provide sleep protection by partner‡; yearly visit for risk reassessment	Potential benefit with home automatic external defibrillator‡ and with bedroom sharing§; yearly visits for risk reassessment

* LQTS type 1 (LQT1) is characterized by a propensity of arrhythmias to develop during physical or emotional stress; type 2 (LQT2) is characterized by a propensity for arrhythmias to develop after loud noises, especially when the person is at rest, and after sleep disruption; and type 3 (LQT3) is characterized by a propensity for arrhythmias to develop when the person is at rest or asleep. Exceptions exist.

† Magnitude of response is indicated by + symbols, ranging from + (the least magnitude of response) to +++ (the greatest magnitude of response).

‡ Access to an automatic external defibrillator at home could be important in severe cases because most events occur when the person is at rest or asleep.

§ Given the horizontal position during sleep and the progressive fall of oxygen perfusion during ventricular tachycardia and ventricular fibrillation, most patients have the time to emit agonic sounds that often allow prompt resuscitation.

stand-up test[52] is of limited value.[50] The epinephrine challenge, proposed when genetic screening was seldom available,[53] has dangerous arrhythmogenic potential and can profoundly alter ventricular repolarization in persons with a normal ECG, and can thus misleadingly suggest the presence of long QT syndrome. As confirmed by the European Society of Cardiology guidelines,[54] epinephrine testing should not be used to make the diagnosis.

THERAPY

The four cornerstones of therapy are beta-blockers, mexiletine, left cardiac sympathetic denervation, and an implantable cardioverter–defibrillator (ICD). These therapies reflect the understanding of the underlying pathophysiology of long QT syndrome. In addition, lifestyle modification, including avoidance of QT-prolonging drugs (a list of these drugs is available at https://www.crediblemeds.org/) and use of potassium supplements (to maintain adequate plasma potassium levels), can contribute substantially to lowering arrhythmic risk.[54]

BETA-BLOCKERS

Since the mid-1970s, beta-blockers have represented the mainstay of therapy for patients with long QT syndrome,[5,55] and their efficacy has been repeatedly confirmed[7,56] independent of the genotype.[57] The only two beta-blockers that have been confirmed to be effective in the syndrome are propranolol (at a dose of 2.0 to 3.5 mg per kilograms of body weight per day) and nadolol (1.0 to 1.5 mg per kilogram per day).[7] Metoprolol should not be used.[58] Nonadherence to beta-blocker therapy and the use of QT-prolonging drugs are responsible for most life-threatening failures of beta-blocker therapy in persons with long QT syndrome.[59]

Beta-blockers should be prescribed also for persons who are genotype-positive–phenotype-negative,[25] with few gene-specific exceptions (e.g., men with long QT syndrome type 1 who are still asymptomatic without therapy at age 25).[40] In

genotype-negative patients with borderline QT prolongation in whom the diagnosis is uncertain, the decision is problematic because once beta-blocker therapy has been started, withdrawing it is difficult, largely for medicolegal reasons.

LEFT CARDIAC SYMPATHETIC DENERVATION

Left cardiac sympathetic denervation, now mostly performed by means of thoracoscopy,[60,61] involves the removal of the lower half of the stellate ganglion to prevent Horner's syndrome[61,62] and of the first four thoracic ganglia (T1 to T4). The rationale for performing left cardiac sympathetic denervation, supported by strong experimental[61] and clinical evidence,[61-63] is largely based on its striking antifibrillatory effect,[64] and includes a major reduction in norepinephrine release at the ventricular level without postdenervation supersensitivity[61] and without heart-rate reduction.[61] Left cardiac sympathetic denervation in a large series of patients consistently showed[63,65,66] an extremely high success rate and, when performed in response to electrical storms (multiple episodes of ventricular tachycardia–fibrillation resulting in appropriate ICD interventions), reduced the annual incidence of ICD shocks by 90%[63,65,67] (Fig. 2), thus preserving a good quality of life.[68] There is a clinically significant QTc shortening in most patients, and this effect is associated with greater long-term protection.[63] The conclusion is that whenever syncopal episodes recur despite full-dose beta-blocker therapy, left cardiac sympathetic denervation should be considered and implemented without hesitation. Given the constantly growing number of centers worldwide that are performing the procedure,[66,69,70] there is no longer justification to implant an ICD in these patients without having first informed them of the pros and cons of left cardiac sympathetic denervation as compared with an ICD.[71,72]

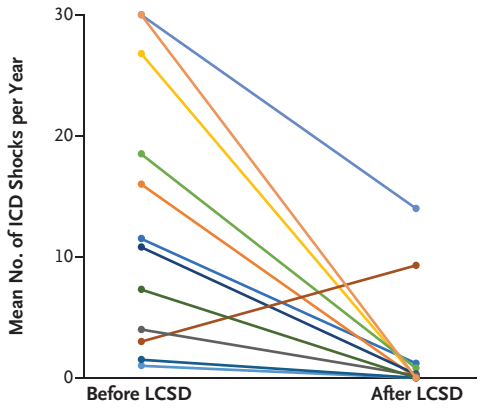

Figure 2. Effects of Left Cardiac Sympathetic Denervation.

Shown are the effects of left cardiac sympathetic denervation (LCSD) on the annual rate of implantable cardioverter–defibrillator (ICD) shocks in 14 patients with long QT syndrome who had recurrent ICD shocks or arrhythmic storms before undergoing LCSD. All 14 patients had more than 1 year of follow-up after undergoing LCSD, 10 (71%) had received at least 10 ICD shocks before LCSD and 11 (79%) were younger than 16 years of age at the time of LCSD.[63,65] These data reflect an overall 90% reduction in the mean yearly number of ICD shocks per patient and a major effect on the patients' quality of life. The number of ICD shocks shown for two patients was capped at 30.

MEXILETINE

In 1995, shortly after the discovery that the *SCN5A* variants causing long QT syndrome were increasing the sodium current,[9,11] the sodium-channel blocker mexiletine was proposed as the first gene-specific therapy for long QT syndrome type 3,[73] and it is now widely used in these patients with the main goal of shortening the QTc and thereby reducing the risk of arrhythmia.[74] Most, but not all, long QT syndrome type 3 variants respond to mexiletine.[75] Recent data show that in almost 70% of patients with long QT syndrome type 2, the QTc is shortened with mexiletine,[76] thus substantially broadening its clinical use. We assess its effect by using the acute oral drug test, which involves the oral administration of mexiletine at a dose of 6 to 8 mg per kilogram, which, within 2 hours, allows the physician to see whether the QTc shortens meaningfully (>40 msec). In this way, only patients in whom there is a positive response to mexiletine are started on long-term therapy.[76]

ICDS

There are large differences in the use of ICDs across the world,[77] with some centers in the United States implanting ICDs in almost 50% of their patients with long QT syndrome, whereas two of the largest clinics in the world treating patients with the syndrome (Mayo Clinic and the Center for Cardiac Arrhythmias of Genetic Origin, Istituto Auxologico Italiano) implant ICDs in approxi-

mately 5% of patients with long QT syndrome.[78] An intravenous ICD is preferable to a subcutaneous one because it allows for pacing, which becomes essential whenever an increase in the beta-blocker dose is necessary, either in patients with a very low heart rate or during arrhythmic storms. Implantation of an ICD immediately after a documented cardiac arrest, either with or without beta-blocker therapy, is reasonable. A study that included 233 patients with long QT syndrome who had received an ICD[67] provided critical information and showed that most of the patients had not suffered a cardiac arrest and, moreover, that many had not had a failure of beta-blocker therapy. Asymptomatic patients, almost absent in the long QT syndrome type 1 and type 2 groups, represented 45% of the patient group with type 3, a finding that indicates that the presence of a pathogenic variant in *SCN5A*, even in asymptomatic persons, was deemed to be sufficient for implantation of an ICD. During a mean follow-up of 5 years, an adverse event occurred in 25% of patients.

There is an excessive use of ICDs in patients with long QT syndrome, and it has been stated that most patients with this disease do not need and should not receive an ICD.[62] Indeed, data on almost 1000 patients with the syndrome show that practically all patients can survive with a minimal use of ICDs when triple therapy (beta-blockers, mexiletine, and left cardiac sympathetic denervation) is implemented with yearly therapeutic optimization.[56] Implantation of an ICD should be recommended in all patients who survive a cardiac arrest while adhering to adequate drug therapy; in patients who have syncope despite receiving full-dose beta-blockers when therapeutic optimization with left cardiac sympathetic denervation and mexiletine is not available; and in all patients with syncope despite receiving a full dose of beta-blockers and left cardiac sympathetic denervation.

NEW PHARMACOLOGIC THERAPIES?

On the basis of experimental evidence, including testing using induced pluripotent stem-cell cardiomyocytes,[79-81] two compounds to treat long QT syndrome are undergoing clinical evaluation. As a result of encouraging preliminary observations,[82] the combination therapy lumacaftor–ivacaftor, already used in the treatment of patients with cystic fibrosis, is being evaluated in the treatment of patients who have long QT syndrome type 2 with trafficking defects. The serum–glucocorticoid regulated kinase 1 regulates cardiac sodium channels, and its inhibition has shortened ventricular repolarization mainly in long QT syndrome type 2 and type 3 models.[80,81] The potential clinical relevance of any of these new therapies will require QTc changes not only to occur in the right direction but also to be of a clinically meaningful magnitude (i.e., shortened by >40 msec).[7,54]

MANAGEMENT

Besides the straightforward implementation of established treatments, the management of long QT syndrome has been substantially refined. Genetic testing offers confirmation and further guidance for gene-specific treatment[40] (Table 2); however, results of genetic screening tests are negative in 10 to 15% of the patients who have long QT syndrome, thus raising questions about their arrhythmic risk and approaches to treatment. Data from 832 patients showed that patients who are genotype-negative–phenotype-positive should be treated in the same way as patients who are genotype-positive–phenotype-positive because their arrhythmic risks are similar.[25]

When results of genetic screening are negative or inconclusive, every effort should be made to ensure that the diagnosis of long QT syndrome is correct. Confirmation should be made by also evaluating QTc behavior during an exercise stress test and 12-lead Holter recording, assessing whether there is the appearance in the T-wave morphologic features of notched or diphasic T waves or of T-wave alternans, and performing a complete cardiac evaluation of the parents, and by suggesting to physically active patients that they adopt a period of detraining to rule out an exercise-induced QTc prolongation.[83]

Important aspects of the clinical management of long QT syndrome are genotype-independent. Long QT syndrome is a moving target in the sense that arrhythmic risk may vary over time and thus require optimization of medical therapy, which usually means the addition of mexiletine or left cardiac sympathetic denervation to beta-blockers (i.e., triple therapy) or implantation of an ICD. Patients should have follow-up visits at least once a year to allow for therapeutic optimization. Recently, the long-term outcomes of

946 patients with long QT syndrome were assessed along with the outcomes that would have resulted if treatment had been based strictly on one of the risk-stratification scores previously proposed to guide treatment in patients with the syndrome.[56,67] On the basis of that risk-stratification score, ICDs should have been implanted in 142 of the 946 patients; however, ICDs were implanted in 22 patients. Only 3 of the patients who received ICDs received an appropriate shock, and no patient died or had a cardiac arrest. Conversely, during follow-up, some patients appeared to be at increased risk for arrhythmias; their therapy was intensified, thereby preventing any arrhythmic episodes. Warnings have been issued[84] about the potential danger in applying risk scores at a patient's initial visit or before the start of therapy (as recommended by the 2022 European Society of Cardiology guidelines[54]), because of the likelihood of excessive and potentially unjustified use of ICDs.[56] Because the initiation of therapy modifies the propensity for arrhythmia, a decision to implant an ICD before a reassessment of risk after therapeutic optimization is not justifiable.[85] Recent data from 2861 patients with long QT syndrome indeed showed that only a minority of those who were candidates for ICD implantation according to the guidelines[54] actually needed an ICD.[78]

An issue especially important for young patients with long QT syndrome is related to participation in sports, which can have a significant psychological effect. The initial very conservative approach is being progressively modified toward a more liberal one,[86] especially for patients with long QT syndrome type 2 or type 3. Decisions regarding participation in sports must include consideration of the fact that in some European countries, participation in sports is regulated by specific laws that sports physicians cannot ignore.

Care should also be exercised to avoid prescribing either one of the least effective beta-blockers or a placebo dose. Bilateral denervation may be necessary in a very small number of patients, but this fact does not justify performing it without first determining whether left cardiac sympathetic denervation is sufficient.[87] Epicardial catheter ablation has been proposed as treatment[88] but has been strongly discouraged[89] because of a lack of substantial and convincing evidence. Indeed, the current availability of therapies that are extremely effective and safe over the long term leaves little room for experimental approaches with weak rationales.

GENE THERAPY

The possibility that gene therapy might help in the treatment of patients with long QT syndrome is an obvious and major interest. However, not all the approaches currently available are feasible.[90] Long QT syndrome involves mainly single-nucleotide variants that affect ion-channel function in different ways, and a successful gene-therapy approach should either silence the variant allele or correct the specific variant through a direct-editing approach.[90] Gene silencing uses several nucleic acids, mainly small RNAs, to target the specific region where the pathogenic variant is present and block the expression of the variant allele. This approach, successfully adopted in vitro in long QT syndrome type 1 and type 2 cellular models,[91-93] has the major limitation of being variant-specific, and the hundreds of variants that cause long QT syndrome would limit its applicability in clinical practice. The same limitation applies to the direct-editing approach.

The recently developed strategy of suppression–replacement therapy[90,94] successfully corrected the long QT syndrome phenotype independent of the disease-causing variant in a number of different cellular models of long QT syndrome type 1[94] and type 2,[90] overcoming a major limitation of the other approaches, and was also validated in a long QT syndrome rabbit model.[95] More recently, the same strategy was used in the treatment of calmodulinopathies.[96]

Major challenges still need to be overcome for the successful translation and implementation of gene therapy into clinical practice for long QT syndrome. Suppression–replacement therapy requires identification of the right dose to be delivered, because undertreatment would not correct the long QT syndrome phenotype and overtreatment could be proarrhythmic. Gene therapies rarely yield a homogeneous population of transduced cells and are associated with a potential for proarrhythmia, owing to the increased heterogeneity of repolarization. There have been

some safety concerns with gene therapy, given the occurrences of adverse events — some lethal — in patients who have received it.[97-99] An additional necessary consideration relevant to the implementation of gene therapy is that long QT syndrome does not increase in arrhythmic risk over time and that current therapy has been associated with extremely low mortality.[56,78] The effectiveness of current therapy greatly reduces the number of patients in need of experimental approaches such as gene therapy, which might be better suited to patients at extremely high risk (e.g., infants who have cardiac events in the first year of life, some with calmodulin variants[19] or variants that cause severe disease [e.g., the p.R1623Q variant in *SCN5A*]) who continue to have appropriate ICD shocks despite full therapy.[41,56]

ACQUIRED LONG QT SYNDROME

The QT interval may become prolonged under several conditions, including hypokalemia, bradycardia, heart block,[100] and, especially, the intake of drugs that share I_{Kr} blocking activity.[101] Acquired long QT syndrome is clinically important because it carries a significant risk for torsades de pointes and sudden cardiac death.[102] Correction of the offending factor prevents recurrences.

The probability of the development of acquired long QT syndrome depends on the intrinsic risk conferred by a given drug, a risk that is mainly dependent on the strength of the I_{Kr} block, and on the individual level of the repolarization reserve,[103] which is modulated by genetic factors.[104-106] This genetic predisposition involves ultrarare,[104] rare,[105] and common genetic variants.[106] The probability of identifying a pathogenic or likely pathogenic variant in patients with acquired long QT syndrome is mainly dependent on three variables: age less than 40 years, QTc (at baseline) greater than 440 msec, and arrhythmic episodes,[104] variables that suggest that sometimes acquired long QT syndrome could unmask a latent congenital long QT syndrome with a low penetrance, as hypothesized in 1982.[107] In the presence of the above-mentioned factors, molecular genetic testing of the definitive disease-associated genes should be offered to patients with acquired long QT syndrome.[23] In addition, two rare variants with functional effect, p.D85N in *KCNE1* and p.S1103Y in *SCN5A*, are consistently associated with acquired long QT syndrome.[108,109] The combination of 61 common genetic variants, all of which influence the QT interval, explains up to 30% of the variability in acquired long QT syndrome.[106] Testing for the presence of common variants is not currently recommended outside of the research setting. Acquired long QT syndrome exemplifies how the combination of genetic and acquired factors can impair repolarization reserve and precipitate arrhythmic events.

Excessive physical training has the potential to induce a marked QT prolongation mimicking long QT syndrome, especially in teenagers, thus favoring diagnostic errors with long-term consequences.[83] Typically, these persons have no family history of long QT syndrome and are asymptomatic and genotype-negative. These abnormalities of ventricular repolarization are reversible with 3 to 4 months of detraining.[83] The arrhythmogenic potential associated with these abnormalities is not clear, but a reduction in the intensity of physical training is needed in order to prevent QT prolongation. Sports physicians should be aware of this phenomenon to avoid prematurely labeling youngsters as having long QT syndrome.

CONCLUSIONS

Long QT syndrome remains an often-lethal disorder for which effective and safe therapies currently exist, thus allowing normal quality of life for almost all patients. Correct management of the syndrome requires specific expertise, and clinicians should be able to suspect the presence of the disease in order to refer patients to a high-volume center with specific experience in treating patients with long QT syndrome.

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