Current perspectives on congenital long QT syndrome

Konjenital uzun QT sendromda güncel perspektifler

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ABSTRACT

Congenital long QT syndrome is a genetic disorder characterized by prolonged QT interval on electrocardiogram and increased risk of sudden cardiac death from ventricular arrhythmias. In long QT syndrome, genes that encode for the various cardiac ion channels or regulatory proteins of these channels are mutated. The various mutations individually lead to a disruption of the normal cardiac myocyte action potential, and thus leading to a propensity for ventricular arrhythmias. Diagnosis can be difficult with patient presentations ranging from palpitations to syncope to sudden cardiac death. The QT interval can also vary over time, often requiring further testing to support the diagnosis. Recently developed genetic testing can be used to identify the responsible genes in patients with known disease. It can also be used to genotype the affected patient's family members. The current test panel only recognizes common mutations resulting in a falsely negative test for those with a rare or unidentified variant. For treatment, beta-blocker therapy is recommended for all patients, and implantable cardioverter-defibrillator (ICD) placement is recommended for those who are at high risk for a cardiac event. Future investigations will concentrate genotype-guided risk stratification for ICD placement and on genotype-specific pharmacological therapy. *(Anadolu Kardiyol Derg 2009; 9: Suppl 2; 3-11)*

Key words: Long QT syndrome, Romano-Ward syndrome, Jervell-Lange Nielsen syndrome, sudden cardiac death

ÖZET

Konjenital uzun QT sendromu, elektrokardiyografide uzamış QT aralığı ile tanımlanan kalıtsal bir hastalıktır ve ventrikül aritmileri sonucu ani kalp ölüm riskini artırır. Çeşitli iyon kanallarını veya bu kanalların düzenleyici proteinlerini kodlayan genler mutasyona uğramıştır. Bu mutasyonların her biri normal kardiyak miyosit aksiyon potansiyelinin bozulmasına yol açar ve böylece ventrikül aritmileri için yatkınlık oluşur. Çarpıntı, senkop ve ani kalp ölümü şeklinde karşımıza çıkan hastalarda tanı güçtür. QT aralığı zaman içinde değişir, genellikle tanıyı desteklemek için ileri testler gerekebilir. Son zamanlarda geliştirilen genetik testler, hastalığı bilinen kişilerde sorumlu genleri tanımlamak için kullanılır. Ayrıca, etkilenen hastanın aile bireylerinin genotiplemesi için de kullanılabilir. Halen kullanılan test paneli güncel genel mutasyonları tanımlar, fakat nadir veya tanımlanamayan varyantlılarda test yalancı negatif sonuçlanabilir. Tedavi için de beta-bloker tedavi tüm hastalara önerilir ve kardiyak olay riski yüksek olanlara da ICD konulması önerilir. Gelecekteki araştırmalar, ICD için genotip-temelli risk stratifikasyonuna ve genotipe özgül tedaviye yoğunlaşabilir.
(Anadolu Kardiyol Derg 2009; 9: Özel Sayı 2; 3-11)

Anahtar kelimeler: Uzun QT sendromu, Romano-Ward sendromu, Jervell-Lange Nielsen sendromu, ani kardiyak ölüm

Introduction

Congenital long QT syndrome (LQTS) is a genetic disorder encompassing a family of mutations that can lead to ventricular arrhythmias and in some patients to sudden cardiac death. The genetic mutations responsible for LQTS are known as "channelopathies." The affected genes encode either directly for protein channels that regulate the flow of sodium, potassium, and calcium ion in and out of the cardiac myocyte or proteins that modify the function of these channels (1). The mutations prolong myocyte action potential resulting in an increased risk of ventricular arrhythmia, specifically torsades de pointes. Torsades de pointes can present with syncope, aborted cardiac arrest, and sudden cardiac death (2-4). LQTS manifests on the patient's

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electrocardiogram as a prolongation of the corrected QT (QT_c) interval and/or abnormal morphology of the T-wave (Fig. 1).

Prior to genetic mapping, LQTS was divided into two syndromes, Romano-Ward syndrome and Jervell Lange-Nielsen syndrome. The two syndromes are differentiated by inheritance patterns and associated non-cardiac defects (5). The Romano-Ward syndrome (RWS) has autosomal dominant inheritance and no associated defects (5, 6). The second, rarer syndrome, Jervell Lange-Nielsen syndrome (JLNS), has autosomal recessive inheritance with bilateral sensory-neural deafness (7, 8). The hearing loss in JLNS results from abnormal potassium ion handling in the inner ear. JLNS patients also have a much greater risk of fatal arrhythmia.

Currently, LQTS is classified according to 11 types of ion channel mutation, LQT1-11, that encompass the prior classification system with some overlap (9, 10) (Table 1). LQT 1-6, and LQT 9-11 correspond to RWS, while LQT 1 and 5 correspond to JLNS when associated with deafness (11). LQT 7, also known as Anderson-Tawil syndrome is associated with periodic paralysis, dysmorphic features, and cardiac arrhythmias (12). LQT 8, also known as Timothy syndrome, is a systemic disorder and is associated with neuro-cognitive impairment, congenital structural heart disease, developmental abnormalities, and immunodeficiencies (13).

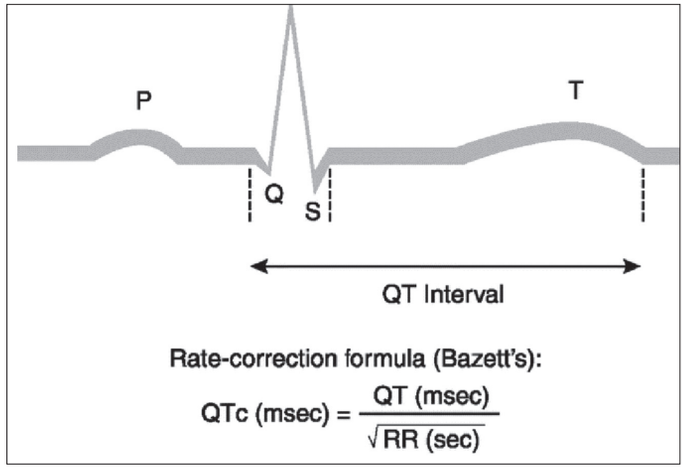

Figure 1. Rate correction for calculation of the corrected QT interval (QTc)

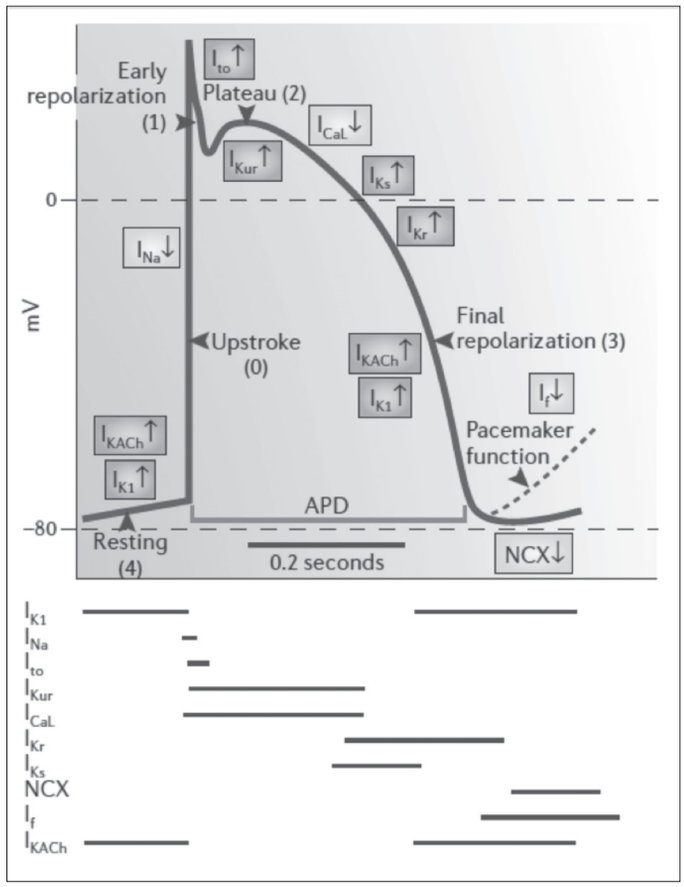

Figure 2. Cardiac depolarization and repolarization, and the ion channels involved with each stage (Reproduced from reference 21 with permission from Nature Publishing Group, Copyright 2006)

Epidemiology

In the United States the incidence of congenital LQTS is estimated to be 1 in 7,000-10,000 (14, 15). There is a female preponderance, ranging from 1.6-2.0:1 (16, 17). Among patients enrolled in the international long-QT registry, the most common presentation was syncope and the average age at presentation was 21±15 years (17). Males with the disease often present during pre-adolescence, while females present later (18). Congenital LQTS is also believed to be one of the causes of sudden infant death, seeming to account for 5-10% of cases (19, 20).

Of the eleven types of channelopathies, the first three, LQT 1-3 are the most prevalent and most studied. LQT1 occurs in 30-35%, LQT2 in 25-30%, LQT3 in 5-10%, LQT4 in 1-2%, and LQT5 in 1% of cases. LQT6-11 are all rare (10).

Pathophysiology

The ventricular myocyte activation cycle, or action potential, is dependent on ion channels (Fig. 2). During rest (phase 4) the cellular pumps in the myocyte membrane push sodium and calcium ions out of the cell and bring potassium ions into the cell. The cell membrane is impermeable to backflow of the sodium and calcium, however, via the inward rectifying potassium channels (I_{K1} and I_{KACh}) the positively charged potassium ions slowly leak out of the cell, leaving the interior negatively charged at -80mV(also known as the membrane potential). As the membrane potential become less negative, it reaches a critical threshold value and the voltage-gated sodium channel, $Na_V1.5$ (I_{Na}), opens allowing positively charged sodium to rapidly flow into the cell. This is phase 0, or depolarization. To maintain this depolarization, L and T-type calcium channels (I_{CaL} and I_{CaT}) are activated to allow the influx of positive calcium ions. During the next phase, phase 1, two types of delayed rectifier potassium channels open to allow efflux of potassium (I_{To} and I_{Kur}), slightly reducing the cells now positive internal charge. During Phase 2, there is equilibrium between influx of calcium and the efflux of potassium and the cardiac myocyte's internal charge plateaus. During phase 3, efflux of potassium ions predominates with the activation of the slow and rapid delayed rectifier channels (I_{Ks}, and I_{Kr}). At the terminal portion of Phase 3, the inward rectifying potassium channels (I_{K1} and I_{Kach}) are

Table 1. Epidemiology, pathophysiology, and management of LQTS based on sub-type

Sub-type	Frequency	Locus	Gene	Ion Channel Defect/ Protein	Mutation Effect	ECG finding	Therapy
LQT1	30-35%	11p15.5	KVLQT1 (KCNQ1)	α-subunit of slowly activating delayed rectifier K^+ channel	↓K^+ Efflux	Broad based t-wave Late-onset t-wave	1. Avoid stress, strenuous exercise and swimming 2. β-blocker 3. ICD if symptomatic on medical therapy 4. Can consider ICD if Qt_c >500 msec (controversial)
LQT2	25-30%	7q35-36	HERG	α-subunit of rapidly activating delayed rectifier K^+ channel	↓K^+ Efflux	Widely split t-wave Low-amplitude t-wave	1. Avoid loud stimuli an stress 2. β-blocker 3. Potassium + Spironolactone (limited data, unclear safety) 4. ICD if symptomatic on medical therapy 5. Can consider ICD if Qt_c >500 msec (controversial)
LQT3	5-10%	3p21-24	SCN5A	α-subunit of voltage gated Na^+ channel	Prolonged Na^+ influx	Late onset t-wave that is biphasic or peaked	1. Avoid loud stimuli an stress 2. β-blocker + ?mexilitene? 3. ICD if symptomatic on medical therapy 4. Can consider ICD in men if Qt_c > 500 msec (controversial)
LQT4	1-2%	4q25-27	ANKB	Ankyrin B adaptor protein that anchors Na^+ -K^+ ATPase and Na^+/$Ca2^+$ exchanger	Build-up of Na+ within cell and $Ca2^+$ outside of cell	Variable Qt interval prolongation	Limited data, probably benefit from β-blocker and then ICD if symptomatic on medical therapy
LQT5	1%	21q22.1-2	Mink (KCNE1)	β-subunit of slowly activating delayed rectifier K^+ channel	↓K+ Efflux	Not defined	Limited data, probably benefit from β-blocker and then ICD if symptomatic on medical therapy
LQT6	rare	21q22.1	MiRP1	β-subunit of rapidly activating delayed rectifier K^+ channel	↓K^+ Efflux	Not defined	Limited data, probably benefit from β-blocker and then ICD if symptomatic on medical therapy
LQT7	rare	17q23	KCNJ2	Inward rectifying potassium channel	↓K^+ Efflux	Mild prolongation of Qt interval Prominent U wave Bidirectional VT	Verapamil? ICD if symptomatic
LQT8	rare	12p13.3	CACNA1C	α-subunit of L-type calcium channel	Prolonged $Ca2^+$ influx	Exaggerated Qt interval prolongation	Verapamil? ICD if symptomatic
LQT9	rare	3p25	CAV3	Caveolin-3 protein	Prolonged Na^+ influx	Not defined	No data, probably benefit from β-blocker and then ICD if symptomatic on medical therapy
LQT10	Extremely rare, found in 1 family	11q23	SCN4 β	β-subunit of voltage gated Na+ channel	Prolonged Na^+ influx	Not defined	No data, probably benefit from β-blocker and then ICD if symptomatic on medical therapy
LQT11	Extremely rare, found in 1 family	7q21-q22	AKAP9	Regulatory protein of α-subunit of slowly activating delayed rectifier K^+ channel	↓K^+ Efflux	Not defined	No data, probably benefit from β-blocker and then ICD if symptomatic on medical therapy

AKAP9 - A kinase anchor protein, ANKB - ankyrin B, $Ca2^+$ - calcium, CAV3 - caveolin 3, ECG - electrocardiogram, HERG - human "ether-a-go-go" related gene, ICD - implantable cardioverter-defibrillator, K^+ - potassium, LQT - long QT interval, msec - milliseconds, Na^+ - sodium

activated, further helping to extrude potassium. This action results in a return of the membrane potential to its negative resting potential. Phases 1-4 are termed repolarization (21-24).

In the various sub-types of LQTS, mutations lead to malfunction of the different ion channels. In all subtypes, the overall effect is a prolongation of repolarization. With the prolonged repolarization, L-type calcium channels can be promoted to re-open causing a rise in cellular calcium. This rise then can lead to a depolarization of the myocyte (early after depolarization) resulting in an extra stimulus (25). Because there is heterogeneity in the repolarization in the surrounding cells, this early beat can then lead to depolarization of neighboring myocytes setting off an unstable ventricular tachycardia, or torsades de pointes (23, 26, 27). Syncope occurs when the torsades de pointes is short-lived and self-terminates, however, if the torsades de pointes does not terminate, it can degenerate to ventricular fibrillation ultimately resulting in sudden death (4).

Sub-Types

LQT1

In this subtype, the protein channel responsible for the slowly deactivating delayed rectifier potassium current, I_{ks} , has a loss of function. The gene that encodes for this protein, KVLQT1 (KCNQ1), is found at locus 11p15.5 (28-30). The I_{ks} channel is composed of 2 types of proteins: one alpha sub-unit and one beta subunit (31, 32). The alpha subunit forms the ion channel while the beta subunit works as a modifier of the channels functioning. The KVLQT1 gene product forms the alpha subunit and mutations in this gene result in reduced I_{ks} current, reduction of potassium efflux (33). The abnormal finding can appear on the electrocardiogram as a broad-based T-wave or a late-onset normal-appearing T-wave (11, 16) (Fig. 3).

LQT2

Mutations in the Human "ether-a-go-go" related gene (HERG) are responsible for this subtype. The locus for HERG is 7q35-36 and encodes for the alpha subunit of the rapidly activating delayed rectifier potassium channel, I_{Kr}.(34, 35). As in LQT1, the channel protein is composed as an alpha and beta subunit. Mutations in this gene lead to loss-of-function of this channel and prolonged repolarization (36). The electrocardiogram can display widely split or low-amplitude T-waves (11, 16) (Fig. 3).

LQT3

Unlike LQT1 and LQT2, the primary mutation in this subtype leads to continued activation of the voltage-gated sodium channel. Mutations in gene SCN5A located on chromosome 3p21-24 lead to a gain-of-function of the channel (34, 37). This mutation prolongs the influx of sodium, extending repolarization (38). The electrocardiogram for these patients will often have late-onset of the t-wave that can be biphasic or peaked (11, 16) (Fig. 3).

LQT4

The genetic mutation in this subtype affects sodium, potassium, and calcium ion flow. Mapped to chromosome 4q25-27, the Ankyrin-B (ANKB) gene encodes for the ankyrin-B adaptor protein (39). This protein is responsible in anchoring the Na-K ATPase and Na/Ca exchanger on the cell membrane (40). Loss of function of these proteins leads to a build-up of sodium within the cell and calcium outside of the cell. The electrocardiogram in these patients shows variable QT prolongation, and they can often have a normal QT interval (11, 16).

LQT5

Similar to LQT1, in this subtype, the slowly delayed rectifier potassium channel (I_{Ks}) also has a loss of function. However, LQT5 is due to mutations of the beta subunit, and it is encoded by minK (KCNE1) gene at locus 21q22.1 (31, 41). As in LQT1, decreased potassium efflux leads to prolonged repolarization(41). A pathognomonic finding on electrocardiogram is not known for this subtype (11, 16).

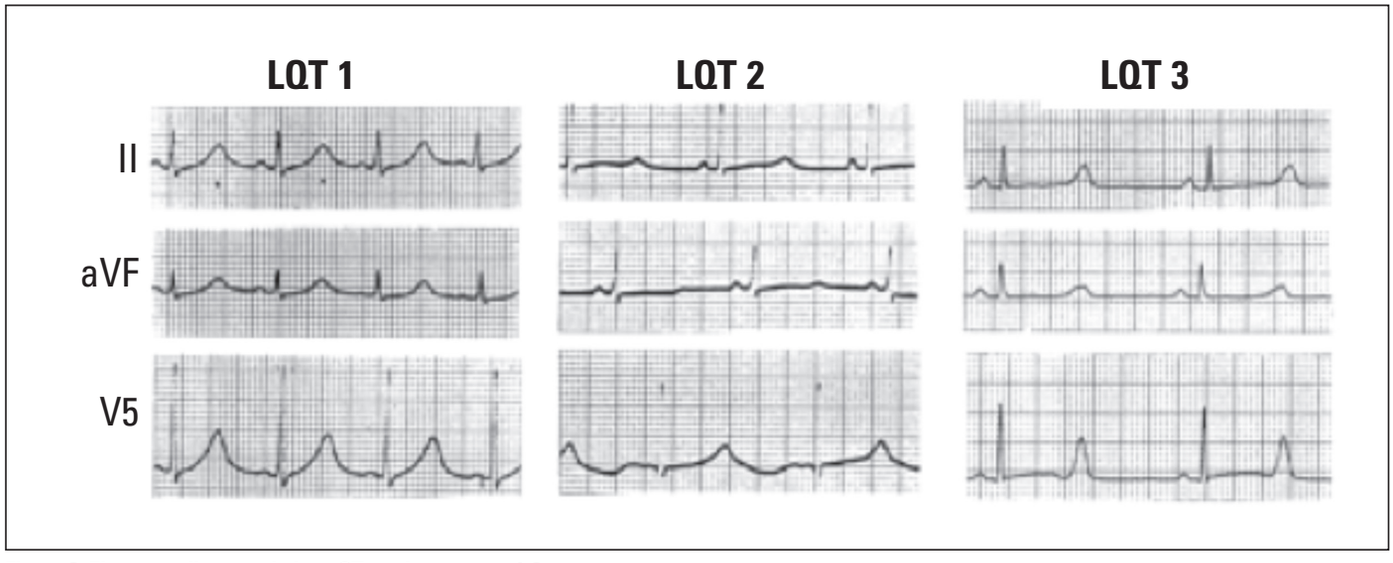

Figure 3. Electrocardiograms in long QT syndrome types 1-3.
(Adapted from reference 83)

LQT6

Mutations of the MiRP1 gene located on chromosome 21q22.1 lead to a loss of function of the beta subunit of the rapid delayed rectifier potassium channel, (I_{Kr}) (42). Similar to LQT2, potassium efflux is decreased and repolarization is prolonged. Electrocardiogram findings have not yet been defined for this subtype (11, 16).

LQT7

In this subtype, also known as Anderson syndrome, there is a mutation of the KCNJ2 gene located on chromosome 17q23. This mutation leads to a loss-of-function of the inward rectifying channel (I_{K1}), resulting in decreased potassium efflux. The electrocardiogram of these patients has a mild prolongation of the QT interval with an exaggerated U-wave. The patients' primary arrhythmia is bidirectional VT (43).

LQT8

In LQT8, Timothy syndrome, inactivation of the L-type calcium channel causes prolonged calcium inflow and markedly prolonged repolarization. The gene responsible for this mutation is CACNA1C and is mapped to chromosome 12p13.3. It encodes for the alpha subunit of the L-type calcium channel, $Ca_V1.2$ (13, 44). The electrocardiogram of these patients can have an exaggerated prolongation of their QT interval (11, 16).

LQT9

As in LQT3, this subtype has prolonged activation of the rapid sodium channel. The gene, CAV3, localizes to chromosome 3p25 and encodes for the Caveolin-3 protein. The Caveolin-3 protein is responsible for forming an invagination in the cell membrane, and the voltage-gated sodium channel co-localizes within the "cave" on the cell membrane (45, 46). Mutations in the CAV3 gene lead to prolonged activation of rapid sodium channel and prolonged phase 0 of the action potential (10). Electrocardiographic findings for this subtype have not yet been defined.

LQT10

The gene, SCN4β, located on chromosome 11q23 encodes for the beta subunit of the voltage-gated sodium channel. Mutations of this gene lead to a gain-of-function of the sodium channel akin to the mutations that cause LQT3 (10, 47). This subtype is very rare, and electrocardiographic findings have not been defined.

LQT11

Most recently discovered, the gene involved in this sub-type, AKAP9, is located on chromosome 7q21-q22. It encodes for the A Kinase Anchoring Protein 9. The AKAP9 protein assembles with the alpha sub-unit of the I_{ks} channel, and is involved in regulation of the channel's proper functioning. A mutation of this gene leads to a loss of function. This sub-type was found in one family previously believed to be genotype negative (48).

Diagnosis

Diagnosis of LQTS is challenging. Patients can be referred for evaluation for many reasons. Symptomatic patients are those with unexplained syncope or aborted sudden cardiac death. Asymptomatic patients can be identified with a prolonged QTc on routine electrocardiogram. Patients can also be referred for evaluation due to the identification of the disease among a first-degree relative. Of note, in both the asymptomatic and symptomatic groups, the QTc interval can be normal on initial presentation (49). Diagnosis among the asymptomatic patients can be especially difficult as they are more likely to have a normal QTc duration then the symptomatic patients (50).

A scoring system has been created to aid in the diagnosis of LQTS (51) (Table 2). A score of ≥4 indicates a high probability of LQTS; 2 or 3 indicates intermediate probability; ≤1 indicates a low probability. A score ≥4 is considered diagnostic. Although using this scoring system does aid in diagnosis, relying purely on this strategy could result in missed diagnosis for the borderline scores. Further testing may be indicated for patients with a low to intermediate score.

One simple test is to repeat the electrocardiogram at various intervals. The QTc interval is not static, and has been found to vary for an individual patients over time (52). By repeating the electrocardiogram, the chance of identifying a prolonged QT interval for a individual with the disease is increased. Stress testing can also be used to aid in the diagnosis, particularly for patients with LQT1. Among patients with LQT1, there is a higher prevalence of "concealed LQTS," or LTQS with a normal QTc. Stress testing with either exercise or an epinephrine infusion can unmask LQT1 by revealing a pathognomonic failure of the QTc interval to shorten with stimulation (53-55).

For the Epinephrine QT stress testing, there are currently two protocols available, the Mayo Clinic protocol and the Shimuzu protocol. The Mayo clinic protocol uses a continuous infusion of epinephrine with a doubling of the dose every 5 minutes. A test

Table 2. Scoring system for the diagnosis of LQTS

Clinical Finding	Points
QTc interval	
≥ 480 msec	3
460-470 msec	2
450 msec, men	1
Torsade de pointes	2
T-wave alternans	1
Notched T-wave in 3 leads	1
Low heart rate for age, children	0.5
Syncope	
With stress	2
Without stress	1
Congenital deafness	0.5
Family member with definite LQTS	1
Unexplained SCD in immediate family member younger than 30 years old	0.5

LQTS - long QT syndrome, msec - milliseconds, QTc interval - corrected QT interval, SCD - sudden cardiac death (Modified from reference 51)

is considered positive when the QT interval increases by ≥30ms at a dose of ≤0.1 μg/kg/min. A positive test is 76% predictive of LQT1. A negative test virtually rules out LQT1, however other subtypes of LQTS cannot be ruled out (54). For the Shimuzu protocol, a bolus of epinephrine is given and then followed by a continuous infusion. If the QTc is prolonged by >35 msec above the baseline during the infusion portion, this is 90% predictive of LQT1. If the QTc interval change does not meet these criteria but is prolonged by greater than 80 msec after the bolus, LTQS2 can be 100% accurately diagnosed (56). It is important to note that with any provocative testing, albeit either exercise or epinephrine infusion, a negative test does not rule out LQTS.

Recently, genetic testing has become commercially available for the diagnosis and sub-typing of LQTS. Genetic testing identifies patients with the most frequent mutations. Currently, it is recommended to perform genetic testing among those clinically diagnosed with LQTS and to test first-degree relatives of patients with known LQTS (9). The test identifies 76% of patients with LQT1-6 (57). It is possible, however, for a patient with LTQS to test negative if the patient's mutation is not included in the panel or if the mutation has not yet been identified (58).

Treatment

Treatment of LQTS is guided by the individual's risk of sudden cardiac death. Patients who have already had an aborted sudden cardiac arrest are considered to have the highest risk of a recurrent event (59). In these patients, medical treatment with beta-blockers and placement of an ICD is strongly recommended (59, 60).

For patients without prior cardiac events, initial therapy is with a beta-blocker medication and lifestyle modifications. This treatment is especially important for those patients with prolonged QTc intervals, as increasing QTc interval is directly related to increased risk of sudden cardiac death (61).

Lifestyle modification includes avoiding triggers of cardiac events and medications that prolong the QT interval. Triggers for LQT1 include stress and exercise, especially swimming. For LQT2, triggers include auditory stimuli and stress. For LQT3, the primary triggers are rest and sleep; hence, there are no specific triggers to avoid (62). For all other subtypes, information on triggers has not yet been defined. Of the three predominant subtypes, LQT3 has the greatest risk of cardiac events at 0.60%/year, followed by LQT2 at 0.56%/year, and LQT1 at 0.30%/year (61).

If patients continue to suffer from syncope and/or ventricular arrhythmia, ICD placement is recommended (60). For those patients at high risk of ventricular arrhythmias, placement of an ICD is life-saving (63). In a study of 27 patients implanted with an ICD, 10 patients (37%) received appropriate shocks and this occurred more frequently in survivors of cardiac arrest, 58% in cardiac arrest patients vs. 20% in non-cardiac arrest patients (64).

There are also special considerations for early ICD implant if the genotype of the patient is known. Current guidelines allow for consideration of ICD placement in patients with LQT2 and LQT3 who are considered to have a greater risk as determined by their genotype, however this is controversial (60). Priori et al. (61) recommends using both QTc duration and gender to further risk stratify these three subtypes. A QTc duration ≥500 msec, portends a higher risk, >50% risk of cardiac event before the age of 40 years old. However, females with LQT3 are not subject to this age stratification, and their risk of a cardiac event is 30-49% (regardless of QTc duration). If the QTc duration is <500 msec, females with LQT 2 and males with LQT 3 have a risk of 30-49% before the age of 40. For all others with a QTc duration <500 msec, the risk of a cardiac events before the age of 40 is <30% and these patients are considered low risk (61).

However, current risk stratification strategies are still limited. Among the highest risk LQTS patients, those with prior aborted sudden cardiac arrest, only 29% had arrhythmic events that were potentially life-threatening on follow-up (65). ICD placement is not without risk and because the devices are implanted in young patients, future generator changes, lead malfunctions and device failures, and lifetime risk of infection and lead extraction need to be considered in the risk-benefit judgment to implant (66-68). In young patients a single ventricular lead is generally preferred because of lower long-term risk (66). Lead placement in the extrathoracic subclavian vein or axillary vein may reduce complications during implantation (69).

Another controversial option for these patients is left cardiac sympathetic denervation (LCSD). This surgical procedure involves removal of nerve plexi that are believed to modulate sympathetic activity on the heart (70). Prior to beta-blockers and ICD's, this surgery was the only non-pharmacologic treatment available. Although LCSD does result in reduced symptoms, almost half of patients who undergo this surgery will have continued events, including sudden cardiac death. Currently denervation is recommended for those with recurrent syncope on medical therapy and those with and ICD who experience arrhythmia storm (71).

With the advent of reliable genetic testing and a better understanding of the pathophysiology of the various mutations, genotype-specific pharmacotherapy is also under investigation. For patients with LQT2, researchers have found that by increasing the extracellular potassium concentration, the QT interval can be shortened. In one small trial, eight patients were given potassium supplementation and spironolactone with a goal potassium 1.5 meq above their baseline. The average potassium level achieved was 1.2 meq above the baseline and all but one patient had significant improvement of their QTc interval. This study was limited by the requirement for frequent blood draws and short follow-up. It is also not known whether this therapy is clinically significant and leads to a reduction in cardiac events (72).

For patients with LQT3, use of mexiletine in conjunction with a beta blocker or ICD has been suggested (73). In a small clinical trial, patients with LQT2 and LQT 3 were placed on mexiletine. Patients in the LQT 3 group had a significant reduction in their QTc interval, while LQT2 patients did not. However, it is not known whether the improvement in the ECG parameters translates to a reduction in cardiac events (74). Also, there is a safety concern using mexiletine in all patients with LQT3 as mexiletene may unmask a Brugada phenotype in specific mutations (75).

For the rarer genotypes, the literature for pharmacotherapy is limited. In case reports, Andersen-Tawil, LQT7, was successfully treated with calcium channel blockers (76, 77). Flecainide has also been used with success in suppressing the bidirectional VT in Andersen-Tawil Syndrome (78-80). LQT8 was successfully treated with calcium channel blockers in two case reports (81, 82)

Conclusion

Future innovation in LQTS will include improved diagnostic algorithms, improved risk stratification strategies, and the development of genotype specific medical therapy. With these steps, the need for ICD therapy should be reduced, leading to a reduction in complications.

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