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Critical Review Article

Long QT Syndrome; Clinical Dilemma from Precise Diagnosis to Management Indications

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Definition

Congenital long QT syndrome (LQTS) is one of the congenital cardiac channelopa¬thies characterized by delayed repolarization of the myocardium leading to prolongation of the QT interval in ECG (QTc > 480 msec as the 50th percentile in genetically confirmed LQTS cohorts). LQTs are associated with an increase risk of ventricular arrhythmias that may lead to sudden death otherwise healthy individual. Various stimuli provoke these episodes depending on the subtype of the condition [1]. Long QT interval can be acquired from different medical conditions and/or administration of certain drugs.

Epidemiology

The incidence of congenital LQTS has been estimated between 1 in 2500 and 1 in 7000 in the general population [2,3]. However, the frequency of LQTS mutations may be considerably greater than these figures due to a low penetrance of congenital LQTS which ranging from 25 to 58 percent on surface ECG when defining LQTS as a QTc > 440 msec in men and 460 msec in women [4]. A study of 817 family members with documented congenital LQTS by genetic testing reports that the average QTc penetrance was only 60 percent [4]. Another study of 199 family members belong to nine families with apparently sporadic LQTS in which no member other than the proband had clinical signs of the disease, found penetrance was only 25 percent, and conventional clinical diagnostic criteria identified only 38 percent of gene carriers [5]. Silent gene carriers and their affected offspring are at risk for developing malignant ventricular arrhythmias such as torsades de pointes, especially if exposed to drugs or other factors that can prolong the QT interval.

Age, gender predominance and SCD risk

Age and gender have been major factors in determining the clinical course and prognosis of congenital LQTS. Patients with LQTS usually have their first cardiac events in childhood, adolescence, or early adulthood. However, LQTS has still been identified in adults as late as in the fifth decade of life [6].

Newly diagnosed cases of LQTS are more prevalent in female patients (60 - 70% of cases) than in male patients. This female predominance may be related to the relatively natural prolonged QTc [7]. On the other hand, the probability of a first cardiac event is higher in males by age 15 but decreases after puberty. Additionally, a relatively higher mortality rate during the first cardiac event was observed in young men [8].

LQTS and pregnancy

Pregnancy is not associated with an increased incidence of cardiac events, whereas the postpartum period is associated with a substantially increased risk of cardiac events, especially in the subset of patients with LQT2. Cardiac events have been highly correlated with

menses. Also, a significantly higher risk of cardiac events (a 3-fold to 8-fold increase, mainly in the form of recurrent episodes of syncope) has been reported in women with LQT2 syndrome during and after the onset of menopause, compared with the reproductive years [9].

Genetics role in LQTS

In contemporary clinical practice, certain genetics panel are employed to identify the culprit gene in high risk LQTS patients. Genetic analysis has great diagnostic and prognostic values in medium to high risk individuals (probands).

To date, common mutations in at least 15 genes are identified. Three major LQTS genes (KCNQ1-encoded I_{Ks} (K_v7.1) potassium channel, KCNH2-encoded I_{Kr} (K_v11.1) potassium channel, and SCN5A-encoded I_{Na} (Na_v1.5) sodium channel) and 10 minor LQTS-susceptibility genes (*CACNA1C*, *KCNJ5, AKAP9, KCNE1, KCNE2, CAV3, SCN4B SNTA1, CALM1, and CALM2)* that account for nearly 80% of the disorder. In addition, three rare gene mutations lead to atypical LQTS or multisystem syndromic disorders associated with either QT or QTU prolongation have been described, namely ankyrin B syndrome (LQT4) caused by mutation in ANK2 gene, Andersen-Tawil syndrome (LQT7) caused by KCNJ2 (ATS1) gene mutation, and Timothy syndrome (LQT8) caused by CACNA1C mutation [10,11].

Clinically there are 13 subtypes of congenital LQTS. The most common genotypes are LQT1 (30-35 percent), LQT2 (25 - 40 percent), and LQT3 (5-10 percent), with the remaining 10 types accounting for < 5 percent of LQTS [3,12]. The inheritance is predominantly autosomal dominant with a clinical phenotype named conventionally as Romano-Ward syndrome which includes LQT1–6 and LQT9–13 and is characterized by an isolated prolongation of the QT interval [13]. Andersen–Tawil syndrome (LOT7) as well as Timothy syndrome (LQT8) are rare subtypes of LQTS which have extra-cardiac manifestations and inherited as autosomal dominance and represent 1% of LQTS, yet quie aggressive gene mutation [14,15]. A less common Jervell and Lange-Nielsen syndrome which combines an extremely prolonged QT interval with congenital deafness is transmitted as autosomal recessive trait.

In addition to that, short QT syndrome (SQTS), which characterized by a reduced duration of cardiac repolarization, constitutes the substrate for the development of life threatening arrhythmias. The disease appears to be highly lethal in all age groups, including children in their first months of life, and the probability of a first cardiac arrest by the age of 40 years is > 40 percent. Five genes have been linked to SQTS (KCNH2, KCNQ1, KCNJ2, CACNA1C and CACNB2b) [13,16].

Different inherited cardiac channelopathies syndromes can overlap. For example Timothy syndrome (LQT8) and Brugada Syndrome are associated with mutations in *CACNA1C* gene, which encode L-type Ca^{2+} gated channels in the α- and β-subunits [17].

Dynamic genetic mutations leading to voltage augmentations occur in few genes, however most genetic mutations, despite novelty, are benign naturally occurring. Thus Functional analysis has provided great prognostic values [14,18].

Clinical Manifestations

The clinical manifestations of congenital LQTS are highly variable. Patients could be asymptomatic or having symptoms in the form of palpitations, presyncope, syncope, seizures, or sudden cardiac death (SCD) [19]. The annual rate of SCD in patients with untreated LQTS is estimated to be between 0.33 and 0.9% [20].

Seizures/Syncopal attacks

Apparent seizure activities can be due to ventricular arrhythmia, typically polymorphic VT. Typically they present as drop attacks/ syncope coinciding with physical activity, sport practice, or emotional stress. However it may have tonic-clonic movements and be misdiagnosed as a primary seizure disorder, often with tragic consequences with potentially fatal consequences [21,22]. Careful history taking could help in differentiation between primary seizure disorder and seizures related to LQTS associated arrhythmias. Emotional stress or physical exertion preceding syncope or seizure may suggest the possibility of LQTS associated arrhythmia [22, 23]. Timing of the loss of consciousness associated with a seizure has been proposed as a risk factor as loss of consciousness before convulsions supports the

possibility of LQTS associated arrhythmia to be the main cause of syncope and/or seizure [24]. ECG screening is indicated in all patients following a first afebrile seizure or unexplained syncope, including episodes consistent with neurocardiogenic (vasovagal) syncope, especially when these episodes are exertional or associated with emotional stress. Seizures episodes at arousal or during sleep should also increase the suspension of underlying LQTS. Those with borderline or prolonged QT intervals should be subjected for further evaluation.

Arrhythmias

Arrhythmias are frequently associated with LQTS presenting symptoms. However, there are different forms of LQTS associated arrhythmias. Polymorphic ventricular tachycardia (VT) is considered the classic arrhythmia; hitherto bradycardia, atrioventricular block, and atrial arrhythmias have been reported in minority of patients.

The report from the Pediatric Electrophysiology Society stated that polymorphic VT, also called torsades de pointes (TdP), was the most common (6 and 9 percent at rest and during an exercise test, respectively), followed by multiform ventricular premature beats (5 percent), uniform ventricular premature beats (4 percent), and monomorphic VT (1 percent). In addition, bradycardia was present in 20 percent and atrioventricular block in 5 percent [25].

Polymorphic VT/torsades de pointes (Tsp.) is a ventricular rhythm ranging from 160 to 250 beats per minute. TdP episodes usually are short-lived and terminate spontaneously or recur in rapid succession and may progress to ventricular fibrillation and cardiac arrest [26].

Bradycardia is a common finding in patients with LQTS, especially children during the first three years of life, fetuses and neonates with LQTS [27]. LQT3 is commonly associated with bradyarrhythmias due to mutations in the cardiac sodium channel gene (SCN5A) causing sinus node dysfunction [28]. Although, atrioventricular (AV) block has been noted in patients with congenital LQTS, high-grade AV block necessitating permanent pacemaker placement is rare.

Atrial arrhythmias such as atrial fibrillation may also be present in patients with LQTS. A report from a single-center cohort of 252 patients with genetically proven LQTS, stated that six patients (2.4 percent; average age 24.3 years) had atrial fibrillation, compared with a prevalence of 0.1 percent among the general population [29].

Clinical syndromes associated with LQTS

The Romano-Ward syndrome is the most common clinical syndrome which characterized by prolonged QTc without extra cardiac manifestations. It is transmitted as an autosomal dominant. A recessive form of the Romano-Ward syndrome with a homozygous mutation in the KVLQT1 gene has been reported [30].

The Jervell and Lange-Nielsen syndrome is an autosomal recessive phenotype of congenital LQTS that is associated with profound sensorineural hearing loss and a high risk for sudden death [31].

Andersen-Tawil syndrome is a rare autosomal dominant disorder identified as LQT7. It is characterized by episodes of paralysis, ventricular arrhythmias, and dysmorphic features include short stature, hypertelorism, a broad nose, low-set ears, and a hypoplastic mandible [32]. The 12-lead ECG reveals QT prolongation, prolonged terminal T wave downslope, biphasic U waves in limb leads, wide T-U junction, and enlarged U waves [33]. LQT7 may present with characteristic bidirectional ventricular arrhythmia [34].

Timothy syndrome is known as LQT8 and is characterized by prolonged QT, syndactyly, cardiac malformations, autism spectrum disorder and dysmorphisms. It has an autosomal dominant mode of inheritance [35].

Sudden infant death syndrome (SIDS) is another example of clinical syndromes associated with LQTS. Mutations known to be associated with LQTS have been identified on post-mortem genetic testing of stillborn fetuses [36].

Turner syndrome, in addition to the structural cardiovascular anomalies, prolongation of the QT interval has been reported. The exact mechanism of the QT prolongation is unknown but does not appear to be directly related to anatomic abnormalities as QT prolongation has been reported in Turner syndrome patients without other structural cardiac disease [37].

Pathophysiology

The pathophysiology of the commonly observed features associated with congenital LQTS is complex and vary among patients. There are different pathophysiological theories that explain the LQTS related features.

LQTS and ion channels potentials

Congenital LQTS is considered a disease of ion channels that is associated with derangements in cardiac ion flows, resulting in an augmentation of the cardiac action potential duration, early after depolarizations (EADs), and triggered activity. EADs, oscillations of the membrane potential that can occur during phase 2 or 3 of the action potential, occur in association with prolongation of the repolarization phase of the action potential. When EADs reach threshold potential, depolarize cell membranes, and result in additional action potentials then they called triggered responses or triggered activity. Propagation of these triggered responses produces ventricular premature depolarizations that may initiate polymorphic VT (TdP) in susceptible subjects [38,39]. EADs and triggered responses are particularly easy to induce in Purkinje fibers and M cells (a group of cells in the left ventricular free wall) [40].

Common Mechanisms of ventricular arrhythmia

1. Increased sympathetic activity, due to increased activity of the left stellate ganglion (innervates most of the ventricular muscles) or reduced activity of the right stellate ganglion, results in increased sympathetic innervation of the heart [41]. Sympathetic stimulation facilitated the induction of TdP by facilitating the induction of triggered activity and early after potentials through decreasing the refractory period, permitting earlier premature stimulation, and/or allowing reentry [42].
2. Other possible mechanisms for the development of LQTC related arrhythmias are dispersion of repolarization (inhomogeneity in repolarization or recovery of excitability in a region of myocardium) and reentry. M cells demonstrate marked prolongation of action potential duration therefore dispersion of repolarization can occur only in M cells but not in the surrounding myocardium. The result is a functional block at the level of M cells region, providing the necessary milieu for the development of a reentrant arrhythmia [43].
3. Congenital LQTS related TdP is pause dependence. It is usually initiated by a "long-short" or "short-long-short" sequence. This beat-to-beat variation is usually caused by ectopic beats. Following an ectopic beat, there is a slight pause in which the RR interval lengthens for one beat (the "long" RR in the sequence). This pause causes the following QT interval to prolong. If, during this lengthened QT interval, a second ectopic beat occurs early (a "short" RR interval), during the vulnerable period of repolarization, torsades de pointes can develop. Data from a study of 62 spontaneous episodes of torsade de pointes among patients with congenital long QT syndrome showed that the majority (74 percent) of documented arrhythmias were "pause dependent"; 82 percent of these pauses were longer than the basic cycle length by > 100 ms. Also, age and sex correlated with the mode of arrhythmia initiation. Arrhythmias in infants (< 3 years old) were not pause dependent, while female sex correlated with pause dependent torsade [44]. Furthermore, Pause-dependent Tdp is common among patients with LQT2, but rare in patients with LQT1 [45].

External triggers for LQTS

Arrhythmias in patients with LQTS are frequently triggered externally by exercise, noise, emotion, even sudden wakening from sleep by an alarm clock, or diving [25]. These triggers are usual daily activities and hence the prognosis for ventricular arrhythmias is eminent. Factors that contribute to the development of acquired LQTS such as electrolyte disturbances (e.g. hypokalemia, hypomagnesemia, and hypocalcaemia), and medications that prolong QT interval (e.g. Class IA antiarrhythmic, class III antiarrhythmic, Ketoconazole, erythromycin, etc.) can provoke arrhythmias in patients with congenital LQTS which is "mild" or previously unknown to the patient.

Genotype specific triggers

There is an association between the triggers that initiate arrhythmic events and the specific genotype of LQTS. For example, exercise is the most common triggering factor for arrhythmic events in patients with LQT1. A study of 371 patients with symptomatic LQT1 (syncope, cardiac arrest, sudden death) stated that LQT1 patients experienced the majority of their events (62%) during exercise [46]. Same study demonstrated that Patients with LQT2 and LQT3 are at highest risk of events when at rest or asleep (68 percent of events), compared with LQT1 in which only 3 percent of events occurred at rest or when asleep. Events related to swimming (occurring either immediately after diving into water or during recreational or competitive swimming activities) may be specific for LQT1 [47]. Acute arousal events (such as exercise, emotion, or noise) are much more likely triggers in LQT1 and LQT2 than LQT3 [46]. In addition, events triggered by auditory stimuli, such as an alarm clock or telephone ringing, are most typically seen in LQT2 [48].

Diagnosis Dilemma

Since the diagnosis of congenital LQTS is not easy given the fact that some genetic mutations associated with it have low penetrance and 2.5 percent of healthy population has a prolonged QT interval. However, in 1993, Schwartz., *et al*. suggested diagnostic criteria/score, revised in 2006 and lastly updated in 2011. The criteria in this diagnostic scoring system are divided to three main categories including ECG findings, Clinical findings, and family history. According to the 2006 and 2011 versions, the probability of having LQTS is rated as low, intermediate, or high for scores of ≤ 1, 1.5 to 3, and ≥ 3.5, respectively [49]. The details of the diagnostic scoring systems are demonstrated in table 1.

ECG findings (in the absence of medications or disorders known to affect these features) QTc (= QT/√RR, interpret with caution with tachycardia since QTc overcorrects at fast heart rates) • ≥480 msec: 3 points • 460 to 470 msec: 2 points • 450 to 459 msec (in males): 1 point QTc at fourth minute of recovery from exercise stress test ≥480 ms: 1 point Torsades de pointes (in the absence of drugs known to prolong QT): 2 points T-wave alternans: 1 point Notched T wave in three leads: 1 point Resting heart rate below second percentile for age (restricted to children): 0.5 point
Clinical findings Syncope (Points for torsade and syncope are mutually exclusive) • With stress: 2 points • Without stress: 1 point
Family history (The same family member cannot be counted in both of these criteria) • Family members with LQTS: 1 point • Unexplained sudden cardiac death in immediate family members <30 years of age: 0.5 point

Table 1: *This table indicate Schwartz score for risk stratifications in LQTS.*

ECG Features

The QT/ QTc intervals and measurements

There is controversy regarding which lead should be used for QTc measurement. Most normal reference ranges are based upon measurements from lead II [50]. However, some suggest using whichever limb lead best shows the end of the T wave [51]; or leads V2 or V3, in which QT measurements are typically the longest [52]; or leads V5 or V6, because of the clarity of the Q-wave onset and T-wave termination.

The QT interval inversely correlates with heart rate; therefore the QT measurement should be adjusted for the heart rate (QTc). The most commonly used rate correction formula is the Bazett's square root; QTc is equal to QT interval in seconds divided by the square root of the preceding RR interval in seconds (QTc = QT interval ÷ √RR interval (in sec). Despite being easy formula, the most important drawback is being inaccurate at heart rate extremes and results in overcorrecting at high rates and under correcting at low ones. The cube root Fridericia formula has the same limitations at slow heart rates, but is considered to reflect a more accurate correction factor in subjects with tachycardia. Linear formulae may have more uniform correction over a wide range of heart rate. The most commonly used linear formula derives from the Framingham study. It may give QTc values that are too low at slow heart rates.

In general, there is no solid agreement on the best formula to be utilized in clinical practice. Most literatures so far endorse that, in resting conditions with heart rates in the 60 - 100 beats/min range, most formulae provide almost equivalent results for the diagnosis of QT prolongation [53].

The normal range for QTc interval is similar in males and females from birth until late adolescence (0.37 to 0.44 sec respectively), however adult females have slightly longer QT intervals than males. A QTc interval of more than 0.45 sec is considered prolonged in men in comparison with 0.47 sec in women, while Figures between 0.43 to 0.45 sec for men and 0.45 to 0.47 sec in women are considered borderline and required further investigations [54].

Approach to Accurate of QT/QTc measurements

Despite all the precautions and the use of QTc interval instead of QT interval, accurate measurement still technically challenging issue due to many factors. First, the presence of a brief isoelectric period in some leads which obscure the beginning of the QRS and lead to underestimation of the QT interval.

Second, the presence of U wave, that makes the identification of the termination of T wave difficult and inaccurate. Inclusion of U wave in the QT interval measurement leads to over diagnosis of LQTS [55]. Clinicians, especially cardiologists, do not include the U wave in the QT interval measurement when it is clearly distinct from T wave. However, it is recommended to include U wave when the T and U waves are merged and/or U wave represents more than 50 percent of the T wave amplitude [51,56].

Third, the variability of RR interval as in case of Atrial Fibrillation (Afib) and sinus arrhythmia, which leads to variable QT interval on a beat-to-beat basis. Averaging the measurement over 10 beats or measuring the QT interval that follow the longest and the shortest RR interval in the ECG then dividing each by the square root of the preceding RR interval and use the average of these two values as the QTc interval can overcome the error resulting from RR interval variability [51].

Fourth most common clinical challenge is QRS prolongation. Because repolarization is the larger component of the entire QT interval, thus QT prolongation is generally considered to reflect abnormalities of repolarization but when depolarization (the QRS complex) is abnormal and prolonged, the significance of mild QT prolongation is uncertain. In such patients, using measurement of the JT interval, defined as the QT interval minus the QRS duration, may be a more appropriate way to identify abnormalities in repolarization [57]. The normal JTc is less than 0.36 sec in children without LQTS and is typically greater than 0.36 sec in children with LQTS [57]. Another approach is to use a threshold of 0.50 sec for a prolonged QTc in the setting of a wide QRS complex [51]. Adjust the QT interval as a linear function to account for QRS duration and heart rate in the presence of wide QRS complex is an accepted approach [58].

Fifth challenge is the variability in QTc duration on repeat ECGs for the same individual during his life. Therefore, it has been suggested that several ECGs recorded over time should be more useful in identifying subjects with abnormally long or short QT intervals than simply one baseline ECG recording [53].

Automated measurement of the QT interval and calculating the QTc in most of ECG machines is another clinical challenge. The accuracy of these automated tools was assessed in a group of 218 subjects in whom simultaneous ECGs were recorded on machines from two different manufacturers; the ECGs were then analyzed with four currently used software packages from the same manufacturers at the time of the analysis [59]. Among the four software packages, the QTc varied by 26 msec (range 406 to 432 msec). The two newer software packages produced more consistent results, but both were notably longer (15 to 26 msec) than older versions that remain in use.

Obviously, gathering all existing tools and measurements will support approaching difficult diagnoses with borderline LQTS/ECGs. Using the T wave morphology, baseline QT and calculated QTc in addition to the automated QTc measurements would all reduce the chance of missing LQTC. However, always clinical presentation adds proportional power to results conclusion.

T Wave morphology changes

T wave morphology is frequently abnormal in patients with congenital LQTS with biphasic or prominent notched T wave being the most described patterns [60]. However a variety of other atypical T wave shapes have also been described in LQTS [61]. T wave abnormal morphological pattern correlate with specific genotypes. The typical patterns, which were demonstrated in a study of 284 carriers of LQTS genes (131 LQT1, 93 LQT2, and 60 LQT3), had the following features: (1) a broad and pronounced T wave or late onset of a normal appearing T wave were seen in 88 percent of LQT1 group; (2) low amplitude T waves or bifid T waves that were obvious, subtle, of low amplitude, or widely split were seen in 88 percent of LQT2 group; (3) 65 percent of LQT3 group had peaked and/or bifid T wave which could be asymmetrically peaked with a steep downslope [61].

T wave alternans (TWA), defined as the regular alternation in T wave amplitude or in polarity, is another ECG abnormality that is associated with congenital LQTS. There are two types; macroscopic TWA which is detected by visual inspection and included in standard diagnostic LQTS score, and microvolt TWA which is a TWA of smaller magnitude and more frequently occurred. There is no significant correlation between TWA and cardiac events [62].

QT/QTc dispersions and its relation with LQTs

QTc dispersion is determined by subtracting the minimum QT interval from the maximum QT interval in 12 leads ECG. QTc dispersions are increased in patients with congenital LQTS. QT dispersion ≥ 55 msec correlated with the development of critical ventricular arrhythmias (ventricular tachycardia, TdP, and cardiac arrest) [63]. Thus ECG measures of dispersion can be useful in stratifying children with the long QT syndrome who are at higher risk for developing critical ventricular arrhythmias.

QTc and Exercise tolerance tests

Typically, the QT interval shortens with exercise and increased heart rate. In contrast, in individuals with congenital LQTS, the QTc interval behaves differently according to gene mutations. Patients with LQT1 have diminished shortening of the QT interval and a reduced chronotropic response during exercise followed by exaggerated lengthening of the QT interval as the heart rate declines during early and late (one and four minutes) recovery after exercise [64]. LQT2 patients have marked QT interval shortening and a normal chronotropic response during exercise followed by exaggerated lengthening of the QT interval as the heart rate declines during late recovery (four minutes) [64]. Patients with LQT3 have a more marked decrease in the QT interval with exercise than either patients with LQT2 or controls [65].

A simple 3-step screening algorithm for detecting LQTS and predicting genotype in asymptomatic first degree relatives of confirmed congenital LQTS patients, based on resting QTc, 4-minute recovery QTc, and 1-minute recovery QTcA was developed in a multicenter study [64].

LQTs diagnosis can be suspected if any of the following conditions observed; (algorithm in Figure 1)

1. If supine QTc; If ≥ 470 ms in males or ≥480 and females,
2. If QTc is normal or borderline normal then check four-minute recovery QTc, four-minute recovery QTc ≥ 445 ms, then probable LQTS, however normal figures indicate probable non-carrier.
3. In probable LQTS, one-minute recovery QTc ≥ 460 ms may suggest LQT1 but figures <460 point towards probable LQT2.

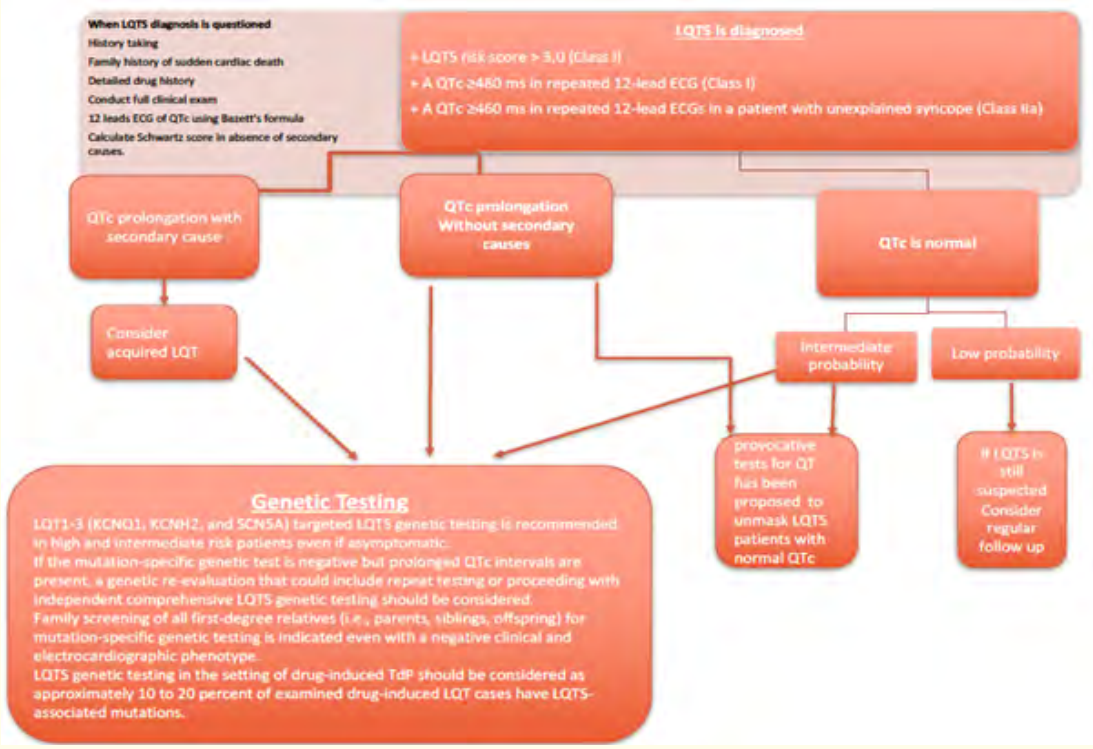

Figure 1: *Screening algorithm for detecting LQTS and predicting phenotype.*

LQTS: Long-QT Syndrome; QTc: Corrected QT Interval; LQT1: LQTS Type 1; LQT2: LQTS Type 2; and n: Number of Patients Investigated with the Current Algorithm

The sensitivity and specificity of the algorithm in the initial cohort were 94 and 90 percent and it was validated in an independent cohort (n = 152) with sensitivity and specificity of 92 and 82 percent. This algorithm may be useful as an interim test while one waits the formal gold stander genetic testing especially in centers where the test is not available [64].

Another clinical value of exercise testing in LQTS is that ventricular arrhythmias such as non-sustained TdP, non-sustained monomorphic ventricular tachycardia (VT), and sustained monomorphic VT may be detected during the test and hence validate the diagnosis [25].

Family history

A detailed family history looks for a history of syncope or sudden unexplained death at a young age in a close relative with documentation of age and mode of death is essential. Consider unexpected events such as drowning in a strong swimmer, or road traffic accidents on

a straight road. Familial epilepsy, sudden infant death, or any sudden unexpected natural death with a negative post-mortem is suspicious and should trigger a family investigation for LQTS and other channelopathies.

Diagnostic tools for LQTS diagnosis

Pharmacologic provocations studies, using drugs such adrenergic agonists (isoproterenol and epinephrine), has found its place in clinical practice based on the fact that approximately 20% - 25% of patients with LQTS, confirmed by the presence of an LQTS gene mutation, may have a normal range QTc. The use of provocative tests for QT measurement during change from a supine to standing position, in the recovery phase of exercise testing, or during infusion of epinephrine has been proposed to unmask LQTS patients with normal QTc at resting ECG as well as distinguish one genetic defect from another [19,66].

Beta-adrenergic agonists, such as isoproterenol and epinephrine, are the most commonly used drugs are [67]. The most important clinical advantages are not causing motion artifacts on the ECG as commonly seen during exercise testing, and can be performed in individuals unable to perform standard exercise testing such as infants, young children, and those with orthopedic injuries. These tests may be considered in uncertain cases based on its ability to unmask LQTS patients with normal QTc at resting ECG, however the clinical use of this test requires more extensive validation [19].

Ambulatory ECG monitoring is sometimes used to help establish the diagnosis of LOTS based on the variability of QT interval and other ECG features of LQTS with activity and time of day [25,68]. Holter monitoring can detect intermittent QT prolongation, T wave notching, macrovolt TWA, ventricular tachyarrhythmia, and bradyarrhythmia [59]. The use of holter monitor in diagnosis of LQTC is very limited because patients without LQTS can often have QT intervals over the normal limits at times, the standards for QTc measurement on ambulatory monitoring are not established, and tape speed may vary on the recording devices resulting in discrepancies in measurements often [69].

Electrophysiology testing including programmed cardiac stimulation is currently not a part of the routine evaluation and management of congenital LQTS as it induces TdP in only about 10 percent of patients with congenital LQTS and inducibility of ventricular arrhythmias has not been predictive of clinical events in congenital LQTS [25].

Genetic testing

Genetic testing to identify specific mutations is now available for clinical use. As a result, genotyping has become more frequently utilized as part of the evaluation of patients with LQTS. Sensitivity of the test is approximately 70 to 75 percent so negative test does not exclude disease especially in the presence of high clinical suspension [19].

Genetic testing recommendations

The 2011 Heart Rhythm Society/European Heart Rhythm Association (HRS/EHRA) expert consensus statement recommends (class I) LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing for any patient with a strong clinical index of suspicion for congenital LQTS based on clinical picture, ECG findings, family history, and/or findings of diagnostic tools such as stress test and provocation tests. In addition, targeted LQTS genetic testing is recommended (class I) for any asymptomatic patient with idiopathic QT prolongation on serial 12-lead ECGs defined as QTc > 480 ms (pre-puberty) or > 500 ms (adults). Asymptomatic patient with otherwise idiopathic QTc values > 460 ms (pre-puberty) or > 480 ms (adults) on serial 12-lead ECGs may be considered (class IIb) for target genetic testing [12].

Family screening of all first-degree relatives (i.e., parents, siblings, offspring) for mutation-specific genetic testing is indicated (class I) when a causative mutation is identified in clinically affected patient [12]. This should be done even with a negative clinical and electrocar-

diographic phenotype as the only way to rule out LQTS in such a family member in cases in which a probable LQTS associated mutation has been established is a negative genetic test. If the genetic test, history, and 12-lead ECG are negative, LQTS is ruled out. However, if the mutation-specific genetic test is negative but prolonged QTc intervals are present, a genetic re-evaluation that could include repeat testing or proceeding with independent comprehensive LQTS genetic testing should be considered. Ideally, clinical and genetic evaluation of distant relatives should extend in concentric circles of first-degree relatives depending on where the LQTS-associated mutation tracks. It may be necessary to include second- and third-degree relatives in the initial genetic screen of relatives.

LQTS genetic testing in the setting of drug-induced TdP should be considered as approximately 10 to 20 percent of examined drug-induced LQT cases have LQTS-associated mutations [12,70]. A 12-lead ECG is recommended for the first-degree relatives.

In the setting of autopsy negative sudden cardiac death with circumstantial evidence points toward a clinical diagnosis of LQTS specifically (such as emotional stress, acoustic trigger, drowning as the trigger of death), genetic screening for LQTS as part of a molecular autopsy may be considered in an attempt to establish probable cause and manner of death and to facilitate the identification of potentially at-risk relatives [12]. In autopsy-negative young sudden death, LQTS diagnosis was proven in 15-20% of cases [71].

LQTS genetic testing should not be performed solely in response to a past history of fainting, as part of pre-sports participation, or as a universal screening protocol. The significant rate of rare variants of uncertain significance (i.e., non-synonymous genetic variation: 4% in whites and 6% to 8% in non-whites) in the LQT1–3 genes complicates correct mutation assignment and mandates that LQTS genetic testing be sought based upon clinical suspicion rather than ordered indiscriminately [12].

Therapeutic and Prognostic values of genetic tests

LQTS genetic testing has therapeutic implications. Beta blocker pharmacotherapy is the primary treatment for the management of most patients with LQTS. Among the three most common genotypes, beta blockers are extremely protective in LQT1 patients and moderately protective in LQT2 [72]. In contrast, targeting of the pathologic, LQT3-associated late sodium current with propranolol (as the preferred beta blocker) and the possible addition of Mexiletine, Flecainide, or Ranolazine represents the preferred pharmaco-therapeutic option for LQT3 [73].

The genetic test had an important prognostic value and it has joined traditional risk factors (i.e., gender, age at onset, QTc at rest, syncope) as independent prognostic risk factors [2]. Compared with the more common potassium channel loss-of-function subtypes (LQT1 and LQT2), patients with LQT3 appear to have the highest mortality per event [47]. In addition, within each of the two major LQTS genotypes (LQT1 and LQT2), the mutation's location within the protein and its functional sequelae have been proposed as independent risk factors with hazards ratios similar to the QTc > 500 ms risk factor [20,74].

Guidelines for LQTS diagnosis

The 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope, based on the HRS/EHRA/APHRS expert consensus statement in 2013, stated that LQTS is diagnosed in the absence of a secondary cause for QT prolongation, by the presence of an LQTS risk score ≥3.5 or QTc ≥500 ms in repeated 12-lead ECG [19,81]. The presence of unequivocally pathogenic mutation in one of the LQTS genes also is enough to confirm the diagnosis [19,81]. The 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death was more conservative and considered the diagnosis of LQTS when either the risk score is > 3.0 or QTc ≥480 ms in repeated 12-lead ECGs [13]. Both guidelines consider LQTS diagnosis (class IIa, level of evidence C) in the presence of a QTc prolongation (480 - 499 ms and ≥ 460ms respectively) in repeated 12-lead ECGs in a patient with unexplained syncope in the absence of a secondary cause for QT prolongation and in the absence of a pathogenic mutation [14,19,81].

Risk stratification

Assessing the risk of developing syncope, malignant arrhythmias and/or sudden cardiac arrest in patients with congenital LQTS is very important. High risk group patients include specific genetic variants including Jervell and Lange Nielsen syndrome and the extremely rare Timothy syndrome (LQT8) which are highly malignant, and manifest with major arrhythmic events very early, and respond poorly to therapies [31,35]. Specific locations, types of mutations, and degree of mutation dysfunction such as mutations in the cytoplasmic loops of LQT1, LQT1 mutations with dominant-negative ion current effects, and mutations in the pore region of LQT2 are associated with higher risk, in contrast concealed mutation-positive patients are at low, but not zero risk for spontaneous arrhythmic events [19,20].

Patients with syncope or cardiac arrest before age 7, especially in the first year of life, have a higher probability of recurrence of arrhythmias and/or lethal events even while being fully protected by the traditional therapies including beta-blockers [75,76]. In addition, patients who suffer arrhythmic events despite being on full medical therapy are at higher risk. The QTc interval has been identified as an independent risk factor. Its length is directly correlates with risk for development of malignant arrhythmias and SCD; the longer the QTc interval the higher is the risk. High risk is present whenever QTc > 500 ms and becomes extremely high whenever QTc > 600 ms [77]. An 18-year-old with a QTc > 550ms has a 19% chance of cardiac arrest by aged 40, compared with a 2% risk if the QTc is less than 470ms [78]. The presence of overt T-wave alternans, especially when evident despite proper therapy, is a direct sign of electrical instability and calls for preventive measures.

Risk factors interact, for example, in a study of 647 patients (386 with a mutation at the LQT1 locus, 206 with a mutation at the LQT2 locus, and 55 with a mutation at the LQT3 locus) who were assessed for the probability of a first cardiac event, defined as the occurrence of syncope, cardiac arrest, or sudden death before the age of 40 years and before the initiation of therapy, patients were classified into three groups; high risk patients (probability of first cardiac event 50% or higher) who included men or women with LQT1 or LQT2 and QTc ≥ 500 ms; men with LQT3 and QTc ≥ 500 ms; intermediate risk group (probability of first cardiac event 30% to 49%) involve women with LQT2 and QTc < 500 ms; men with LQT3 and QTc < 500 ms; women with LQT3 (irrespective of level of QTc prolongation); low risk patients (probability of first cardiac event < 30%) who included men or women with LQT1 and QTc < 500 ms; men with LQT2 and QTc <500 ms [20].

Another example for this interaction is among genotyped patients, LQT1 males, who are asymptomatic at a young age, 37 are at low risk of becoming symptomatic later on in life, while females, and especially LQT2 females, remain at risk even after age 40 [8].

Management Rational

After revision of the most recent HRS/EHRA/APHRS expert consensus statement in 2013, the 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, The AHA/ACC/ESC guidelines for LQTS therapy which published in 2006, and 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope, the management rational for LQTS includes:

Removal of triggers and life-style modifications

Guidelines agreed to consider the following lines of treatment as a class I indication (level of evidence B) in all patients with LQTS; 1) Removal of triggers and life-style modifications, such as avoidance of strenuous exercise, especially swimming, without supervision in LQT1 patients and reduction in exposure to abrupt loud noises (alarm clock, phone ringing, etc) in LQT2 patients. 2) Avoidance of drugs that prolong QT interval. 3) Identification and correction of electrolyte abnormalities which may occur during different medical illness such as diarrhea, vomiting, metabolic conditions or imbalanced diets for weight loss, is essential [13,19,80,81].

Regarding the safety of participation of LQTS patients in competitive sports, it is still a matter of debate due to lack of enough information. Based on recently available retrospective data which needs more confirmation, low-risk patients, with genetically confirmed LQTS

but with borderline QTc prolongation, no history of cardiac symptoms, and no family history of multiple sudden cardiac deaths (SCD), may be allowed to participate in competitive sports in special cases after full clinical evaluation, utilization of appropriate LQTS therapy and when competitive activity is performed where automated external defibrillators are available and personnel trained in basic life support [19,79]. Competitive sport should be avoided in patients genotyped as LQT1, having high risk features, and/or with exercise induced symptoms [19].

Beta blockers

There is a strong agreement between all guidelines on the following statement; beta-blockers, unless contra-indicated, are class I indicated (level of evidence B) as a first line treatment in patients with asymptomatic LQTS and QTc ≥470 ms and/or symptomatic for syncope or documented ventricular tachycardia/ventricular fibrillation (VT/VF) [13,19,80,81]. Beta-blockers can be useful (class IIa, level of evidence B) in patients with a diagnosis of LQTS who are asymptomatic with QTc ≤470 ms.

Both cardioselective and noncardioselective beta-blockers can be used, however the cardioselective ones are preferred in those patients who suffer from asthma. Long-acting beta-blockers such as Nadolol or sustained-release propranolol should be preferred as these medications can be given once or twice a day with avoidance of wide fluctuations in blood levels [19,76]. Nadolol may have a superior protective effect to other beta blockers in long QT type 2, and may be the most effective at preventing first cardiac events in LQT1 and LQT2, and propranolol may be least effective in those with prior cardiac events [82,83]. It is recommended to titrate up the dose of beta blocker agent to full dosing for age and weight, if tolerated [19]. Sudden discontinuation of beta-blockers should be avoided as this may increase the risk of exacerbation due to up-regulation of beta-receptors on treatment [19].

The response to beta blockers depends on the genotype. Overall reduction of risk of sudden cardiac death by beta blockers in high risk subjects is 67% in LQT1 males and 71% in LQT2 females [84]. This effect may be even higher if long-term compliance is assured. No benefit is yet firmly established with long QT 3, though it has been suggested to reduce risk to one third, particularly in women, by a multinational registry report which not yet in full publication [85].

Implantable Cardioverter Defibrillators (ICD)

ICD therapy is indicated (class I with level of evidence B) in LQTS patients who are survivors of cardiac arrest [13,19]. ICD implantation in addition to beta-blockers should be considered (class IIa/B) in LQTS patients who experienced syncope and/or VT while receiving an adequate dose of beta-blockers [13,19]. Prophylactic ICD therapy may be considered, on an individual basis, in high-risk patients such as women with LQT2 and QTc >500 ms, patients with QTc >500 ms and signs of electrical instability, and patients with high-risk genetic profiles (carriers of two mutations, including Jervell and Lange–Nielsen syndrome or Timothy syndrome) [13,19,31]. Implant of an ICD may be considered (class IIb with level of evidence C) in addition to beta-blocker therapy in asymptomatic carriers of a pathogenic mutation in KCNH2 or SCN5A when QTc is >500 ms [13].

ICD implantation is not indicated (class III) in asymptomatic LQTS patients who have not been tried on beta-blocker therapy. For example, LQTS-related sudden death in one family member is not an indication for ICD in surviving affected family members unless they have an individual profile of high risk for arrhythmic events as mentioned before [19,86].

Complications of ICD therapy, such as inappropriate shocks, need for revisions, lead dislodgement/ fracture and change in capture/ sensing/defibrillation thresholds, are not infrequent especially in the younger age group. Risk/benefit considerations should be carefully considered before initiating this invasive therapy. Accordingly, the decision to have an ICD implanted should be made only after a careful consideration of (1) risk of sudden death; (2) the short- and long-term risks of ICD implantation; and (3) values and preferences of the patient [19]. Infants and pediatric patients with LQT1, who experience a cardiac arrest while not receiving beta-blockers, may only be treated with beta-blockers or with LCSD in settings when the implant of an ICD is likely to be associated with high risk [19,87,88]. Among

those receiving primary ICDs, women (post pubertal females) with long QT type 2 and significant QT prolongation, are the most likely to receive an appropriate discharge.

Whenever ICD therapy is chosen, thoughtful programming (in particular to prevent inappropriate shocks due to tachy- and brady-arrhythmias or ventricular tachycardia which would likely self-terminate) is pertinent and usually requires a VF-only zone, with a cutoff rate greater than 220 - 240 bpm [19]. In addition, subcutaneous ICD systems should be considered if there is no indication for pacing, as these systems avoid the risks associated with transvenous leads [82].

Left Cardiac Sympathetic Denervation (LCSD)

Minimally invasive left cardiac sympathectomy should be considered (class IIa with level of evidence C) in patients with symptomatic LQTS in the following situations; (1) Beta-blockers are either not effective in preventing syncope/arrhythmias, not tolerated, not accepted or contraindicated; (2) ICD therapy is contraindicated, for example, very-high risk infants and children in whom ICD therapy may be relatively contraindicated due to the physical size of the patient, or refused by the patient; (3) Patients with a diagnosis of LQTS who experience breakthrough events while on therapy with beta-blockers/ICD [13,19,80-82]. However, LCSD alone does not completely prevent cardiac events, including SCD, during long-term follow-up [81].

LCSD may be considered in LQT3 or a personal or family history of events during rest or sleep based on the fact that LQT3 patients are at higher risk at slower heart-rates, and the QT interval shortens at faster heart-rates. This raises concerns regarding the use of beta blockers in this group. The prevention of noradrenaline release remains important, but it may be more safely achieved with selective left cardiac sympathetic denervation, which does not reduce heart-rate [82].

The procedure can be done surgically through a left supraclavicular incision or as a minimally invasive procedure in experienced centers. Pneumothorax and left ptosis are uncommon complications when performed using video-assisted thoracic sympathectomy. Asymmetrical facial flushing and sweating is more common, as is dryness of the left hand and profuse sweating of the right hand [82,89].

Other therapies

Sodium channel blockers (Expletive, Flecainide or Granulizing) may be considered (IIb/C) as add-on therapy to shorten the QT interval in LQTS3 patients with a QTc >500 ms especially those who are refractory to beta-blockers or in patients with recurrent events despite ICD and LCSD therapies when there is a shorten of their QTc by 440 ms following an acute oral drug test with one of these compounds [13,19]. The use of these agents is usually carried out on an observational trial basis, with, occasionally, some dramatic results for individual subjects. Follow-up experience with these therapies is limited. No general recommendations can be made at this time in the use of gene-specific therapies [19].

Cardiac pacing may be beneficial in patients with LQT3 who remain symptomatic despite beta blockers, particularly those in whom bradycardia facilitates TdP (pause-dependent arrhythmias) [19,90]. The use of cardiac pacing allows the safe use of beta blockers. Dual chamber pacing is the recommended mode due to the risk of having atrioventricular (AV) block, especially with the use of maximum tolerated dose of beta blockers [90,91]. A study of 37 patients with idiopathic long-QT syndrome who were treated with combined therapy consisting of continuous cardiac pacing and maximally tolerated beta-blocker therapy reported that 28 of 37 patients remain without symptoms with beta-blocker therapy and continuous pacing throughout the study follow up period. The incidence of SCD or aborted cardiac arrest was 24 percent overall and 17 percent in those who continued to take beta blockers. Authors concluded that, combined therapy appears to provide reasonable, long-term control for this high-risk group, however the high mortality in patients with recurrent syncope or TdP while on beta blockers strongly suggests the use of a “back-up” defibrillator, particularly in noncompliant adolescent patients [91].

Invasive EPS with PVS is not recommended (class III) for SCD risk stratification or as a line of treatment in patients with congenital LQTs as there is no data supporting any prognostic or therapeutic values [13].

Asymptomatic Family Members

For those family members who are genotype confirmed, but are asymptomatic, some risk reduction is warranted. Regardless of QTc length, all individuals should avoid medications contra-indicated in LQTS. Those with a long QT interval (> 500ms), especially young males and adult females need to be treated. The role of beta blockers in those without symptoms, a normal QT interval yet a positive genetic diagnosis is controversial. Intuitively, those with a family history of adrenergic induced cardiac events or known to have LQT1 are most likely to benefit. Risk of life threatening arrhythmia is 4% by age 40 years in this group. This compares to 0.4% in gene negative family controls. However two-thirds of these subjects had warning syncope prior to potentially lethal arrhythmia, and thus would, under appropriate surveillance, have been started on therapy. Death under age 10 is very rare (one LQT3 infant among 3,386 genotyped subjects) [82,92].

Clinical approach for suspected LQTS based on guidelines recommendations

For simplified clinical use we proposed an algorithm based on guidelines recommendations [12,13,19,80,81]. We believe this algorithm will help risk stratify SCD of suspected patient with LQTS (Figure 1).

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