The Long-QT Syndrome: A Silent Killer

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CLINICAL POINTS

- The long-QT syndrome can be inherited or acquired.
- It affects the function of cardiac ion channels and is characterised by a prolonged QT-interval on ECG.
- High risk individuals, including those with a suggestive history and/or ECG and those with an affected 1st-degree relative, and athletes should undergo screening.
- Prophylactic treatments available include lifestyle modification, beta-blockade, gene-specific therapies, LSCD and ICDs.
- Research must continue to uncover all gene-mutations causing SCD in order to improve the diagnosis and management of those at risk.

ABSTRACT

Introduction: Sudden cardiac death is a striking phenomenon, affecting seemingly healthy individuals without warning. The long-QT syndrome is a common cause of sudden cardiac death that can either be inherited or acquired. While congenital long-QT syndrome comprises a heterogeneous group of hereditary disorders affecting ion channels in the heart, acquired long-QT syndrome is usually a result of pharmacological therapy.

Main Body: Various mutations in twelve different genes have been linked with the long-QT syndrome to date. This condition is characterised by a prolonged QT-interval on ECG, which signifies a delay in ventricular repolarisation. The clinical presentation of this syndrome can range from symptoms of dizziness and syncope to sudden death. Diagnosing long-QT syndrome is difficult due to variable penetrance in its inheritance and the existence of yet unidentified causative mutations.

Discussion and Conclusions: Accurate diagnosis of the long-QT syndrome is essential as this condition may predispose an individual to sudden cardiac death. Prophylactic therapy for the syndrome exists and therefore early identification of those at risk is crucial in reducing the number of preventable cardiac deaths. Research must continue to discover all mutations responsible for sudden cardiac death so that therapeutic strategies can be developed to combat this silent killer.

Introduction

Sudden cardiac death (SCD) is unexpected death due to cardiac causes usually occurring within an hour of the onset of symptoms [1]. Often the individual is previously well, with no knowledge of an underlying cardiac condition. SCD in young people, particularly athletes, is an issue that has come to public attention in recent years. More than 5,000 people suffer from SCD each year in Ireland, 15% of who are under the age of 35 [2]. Globally, SCD is thought to affect 4-5 million people per year [3]. Screening programmes are now available in Ireland and elsewhere, targeting those thought to be at risk of SCD. Although many causes such as coronary artery disease, cardiomyopathies and cardiac conduction defects have been recognised, in many cases, the cause of death cannot be established and grieving families are left without answers.

Congenital long-QT syndrome (cLQTS) is the most common hereditary cause of sudden arrhythmic death; underlying 23-28% of cases [4]. The first data-based estimate of the global prevalence of cLQTS was published recently by Schwartz *et al.* [7], estimating that it is present in 1 in every 2,500 live births. This condition is comprised of a group of heterogeneous disorders that differentially affect ion channels and proteins that regulate the cardiac cycle [5, 6]. More common than its congenital counterpart is acquired long-QT syndrome (aLQTS) [5, 6, 8]. This form of the condition mainly results from pharmacological therapy [6]. Hormone and electrolyte disturbances such as hypothyroidism and hypocalcaemia have also been implicated.[5]

This paper provides a brief overview of data accumulated to date on the genetics, pathophysiology, diagnosis and management of LQTS. It also serves to illustrate the need for continued research in order to identify all mutations responsible for the syndrome which will ultimately allow for the improved diagnosis and treatment of those at risk.

Genetics of Congenital Long-QT Syndrome

Much progress has been made in the last decade in uncovering the genetic basis of cLQTS. In excess of 600 different mutations have been identified in twelve genes that result in this disorder (Table 1) [9, 10]. On this basis, twelve subtypes are currently

Sub-type	Incidence (%)	Gene	Protein	Effect of mutation	Triggers of cardiac events	Syndrome
LQT1	45	*KCNQ1*	KvLQT1α	↓ IKs	exercise, swimming	RW JLN
LQT2	45	*KCNH2*	HERG α	↓ IKr	sudden noise, emotional stress, postpartum period	RW
LQT3	8	*SCN5A*	Nav1.5	↑ INa	rest/sleep	RW
LQT4	1	*ANK2*	Ankyrin B	disrupts cardiac ion channel distribution	exercise, emotional stress	RW
LQT5	<1	*KCNE1*	β-subunit minK	↓ IKs		RW JLN
LQT6	<1	*KCNE2*	β-subunit MiRP1	↓ IKr		RW
LQT7	<1	*KCNJ2*	Kir2.1	↓ IK1	altered serum K^+ levels	Andersen-Tawil
LQT8	<1	*CACNA-1C*	Cav1.2	↑ ICa	sepsis, hypoglycaemia	Timothy
LQT9	<1	*CAV3*	Caveolin-3	↑ INa		RW
LQT10	<1	*SCN4B*	Navβ4	↑ INa		RW
LQT11	<1	*AKAP9*	A-kinase anchor protein-9	↓ IKs		
LQT12	<1	*SNTA1*	α1-syntrophin	↑ INa		

Table 1: Existing Subtypes of the Long-QT Syndrome [6-8, 13-25]

Legend
RW Romano-Ward syndrome
JLN Jervell-Lange Nielsen syndrome
IKs Slow component of the delayed rectifier K+ current involved in cardiac cell repolarisation
IKr Rapid component of the delayed rectifier K+ current involved in cardiac cell repolarisation
INa Na+ current involved in cardiac cell depolarisation
IK1 Inward rectifier K+ current involved in cardiac cell repolarisation
ICa Ca2+ current involved in cardiac cell depolarisation

thought to exist (LQT1-LQT12). LQT1, LQT2 and LQT3 are the most common. Together, they account for approximately 98% of all genetically characterised cases [6, 8].

Several variants of cLQTS have been described. The most commonly reported is the autosomal dominant Romano-Ward syndrome (RW), although a rare autosomal recessive variant, Jervell-Lange Nielsen syndrome (JLN), was the first to be described in 1957 [11]. The principle difference between these two conditions is that JLN is additionally associated with congenital sensorineural deafness and has a higher risk of sudden death than RW [5, 8, 11]. Furthermore, the inheritance of RW is not strictly mendelian; females are affected to a slightly greater extent [12]. Rarer still are variants such as Andersen-Tawil syndrome and Timothy's syndrome.

Pathophysiology of the Long-QT Syndrome

The pathological mechanism is different for each of the cLQTS subtypes, yet all have the same overall effect of delaying ventricular repolarisation through the retention of positively charged ions (K^+, Na^+, Ca^{2+}) in myocardial cells [8]. This creates electrical instability and predisposes to the ventricular arrhythmia *torsades de pointes* (TdP) (Figure 1). Although TdP resolves spontaneously in the majority of cases, a minority of patients will degenerate into ventricular fibrillation following TdP [8, 26]. Without immediate defibrillation, this can lead to SCD.

Acquired LQTS, as previously mentioned, can result from certain drug therapies, many of which are in common use. They include the antibiotics erythromycin, clarithromycin and suxamethoxazole; the anti-histamines terfenadine and oxatomide; and the anti-arrhythmics amiodarone, sotolol and quinidine [27]. These agents may block KCNH2 potassium channels causing a delay in cardiac repolarisation in a manner similar to cLQTS. A subset of patients with aLQTS were subsequently found to have an underlying genetic suscep-

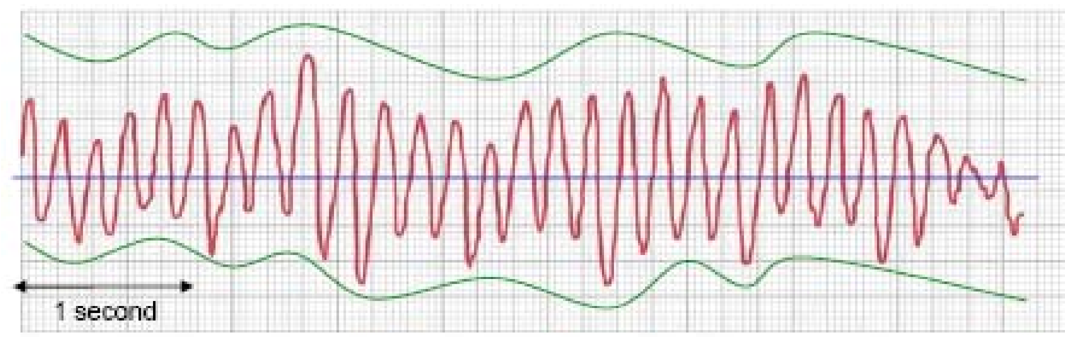
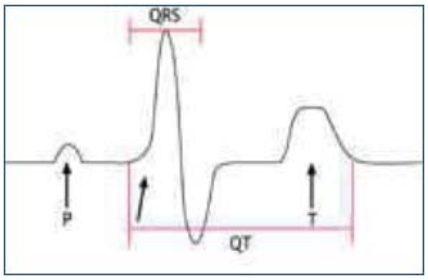
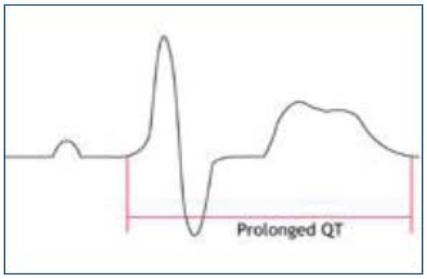


Figure 1: ECG recording showing an episode of the polymorphic ventricular arrhythmia torsades de pointes ("twisting of the points"). The curvy green lines show the characteristic "twist" of the QRS complexes around the isoelectric baseline in blue (adapted from Ashley and Niebauer, 2004) [27].



▲ **Figure 2a:** Normal ECG pattern depicting electrical activity of the heart as it contracts and relaxes. The QT-interval (beginning of the QRS complex to end of the T wave) is a measure of the duration of ventricular depolarisation and repolarisation.



▲ **Figure 2b:** Typical ECG of a LQTS patient. The QT-interval is prolonged and so the duration of the action potential is lengthened and repolarisation is delayed. (Adapted from "Cardiac Risk in the Young. SADS sudden arrhythmic death syndrome"[33])

tibility, having been silent mutation carriers until they were administered these drugs [4]. Evidently, physicians should exercise caution when prescribing these drugs, particularly when co-prescribing them as this would further increase the risk of arrhythmia.

Diagnosing the Long-QT Syndrome

The diagnostic methods available for LQTS can mainly be divided into clinical- and molecular-based methods. LQTS largely remains a clinical diagnosis made by detailed history-taking and ECG interpretation. The discovery of all LQTS mutations could ultimately alter this practice however to favour a molecular-based approach.

History

Congenital LQTS usually presents by the age of forty [4]. Common presentations include palpitations, dizziness, syncope, seizures and sudden death. Cardiac events can be precipitated by different activities, depending on the subtype involved. Exercise, particularly swimming, can trigger events in LQT1 whereas rest and sleep are triggers in LQT3 (Table 1) [8, 25, 26]. A detailed personal and family history enquiring about the circumstances surrounding cardiac events is therefore essential to recognise the syndrome and to deduce the likely genotype involved.

Electrocardiography

ECG is another important method used for diagnosing LQTS. As described earlier, LQTS causes a delay in ventricular repolarisation. This is signified on ECG by a prolonged QT-interval. A QT-interval corrected for heart rate (the QTc) using Bazett's formula ($QTc_{(ms)} = QT_{(ms)} / \sqrt{R\text{-}R}$, where R-R (sec) is measured from the onset of one QRS complex to the onset of the next) is considered prolonged if it measures ≥460 ms in a female or ≥440 ms in a male (normal range 380-440 ms) [5, 28]. In addition, it is important to recognise other ECG findings that can also indicate a diagnosis of LQTS as 25-35% of mutation carriers have a QT-duration of <440 ms due to incomplete penetrance and these individuals should not be overlooked [29, 30]. Moreover, up to 15% of the healthy population have a QTc in the 'borderline range' of 440-470 ms [31, 32]. Distinct T-wave patterns and poor accommodation of the QT-interval in response to an increased heart rate are also considered positive findings associated with the condition [5, 28]. The latter is noted upon exercise or epinephrine challenge testing [8, 29].

Diagnostic Criteria

The Schwartz diagnostic criterion is useful in the initial evaluation of a patient suspected of having cLQTS [28]. Points are allocated to various clinical, familial and ECG findings. Points for positive findings are added together to give an overall score that indicates the probability of a positive

		Points
ECG findings [a]		
QTc [b]	>480 ms	3
	460-470 ms	2
	450 ms (male)	1
Torsades de pointes [c]		2
T wave	T -wave alternans	1
	Notched T-wave in 3 leads	1
Low heart rate for age [d]		0.5
Clinical history		
Syncope	With stress	2
	Without stress	1
Congenital deafness		0.5
Family history [e]		
A	Family members with definite LQTS	1
B	Unexplained sudden cardiac death below the age of 30 amongst immediate family members	0.5

▶ **Table 2:** 1993-2006 LQTS Diagnostic Criteria [8, 28, 30]

Score < 1 point = Low probability of LQTS
1-3 points = Intermediate probability
>3-5 = High probability

a In the absence of medications or disorders known to affect these ECG findings

b QTc (the corrected QT interval) calculated by Bazett's Formula where $QTc = QT/\sqrt{R\text{-}R}$

c Mutually exclusive

d Resting heart rate below 2nd percentile for age

e The same family member cannot be counted in A and B

diagnosis (Table 2). With an intermediate probability, serial ECGs and 24-hr Holter monitoring should be done as the QTc can vary over time [30]. The ECG abnormalities previously mentioned should also be sought.

Molecular Diagnosis

Although genetic screening is considered the gold standard for diagnosing cLQTS, clinical diagnostic methods are largely regarded as sufficient in identifying affected individuals [5, 8]. Reasons for this are that screening is restricted by cost and time. A false negative rate of 30-35% [30] also limits its widespread use. Screening does however provide useful information where a previously reported mutation is implicated. In these instances, it is more useful than history and ECG at identifying the patient's genotype which strongly influences their risk stratification and management decisions.

In 1999, the European Working Group on Arrhythmias [34] recommended the use of genetic screening where it might: i) confirm diagnosis for an individual with borderline clinical criteria; ii) alter the management of a clinically diagnosed individual; or, iii) identify affected, asymptomatic first-degree relatives of a diagnosed patient. Variable penetrance means that asymptomatic family members cannot be regarded as being unaffected without being excluded from carrying a mutation. The proband should first be screened and their mutation identified. This will then allow for efficient screening of first-degree relatives and for the prophylactic treatment of those found affected [5].

Ideally all 12 LQTS genes should be screened when evaluating a patient for LQTS. However, this is not practical considering how rare some of the syndrome subtypes are as well as the cost and time involved. Different laboratories have their own protocols for screening varying numbers of the genes. Regions of the LQT1, 2, 3, 5 and 6 genes known to harbour LQTS-mutations are usually screened [35].

Limitations of Diagnostic Methods used for the Long-QT syndrome

Accurate diagnosis of LQTS is crucial given that it is a potentially lethal disorder for which prophylactic therapy exists. However, as with many diagnostic techniques, each of those used for the syndrome has limitations. The use of ECG as a diagnostic tool for LQTS has several shortcomings. The QTc is commonly miscalculated [36] and the potential exists for false positives and false negatives using current QTc cut-off lengths. Also, Bazett's formula may lead to over- or under-correction of the QT-interval at slow or fast heart rates respectively.[28] Genetic screening is not always reliable as not all LQTS-mutations are yet known. The overall message conveyed is that none of the diagnostic techniques currently available can be fully relied on and so history and examination should guide the physician's suspicions and the degree of evaluation needed.

Differential Diagnosis

The main conditions from which cLQTS must be distinguished are those affecting the structure of the heart and those affecting the cardiac conduction system. These conditions include; hypertrophic obstructive cardiomyopathy, dilated cardiomyopathy, aLQTS, catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic right ventricular cardiomyopathy and Brugada syndrome [5, 28]. Non-cardiac differentials that should be considered include vasovagal syncope, situational syncope, orthostatic hypotension and epilepsy, depending on the symptoms reported.

Recommendations	Level of Evidence*	Comment
Avoid participation in competitive sports	I	For both clinically and genetically diagnosed patients
Beta-blockers	I	For patients with a prolonged QTc (>440 ms in a male and >460 ms in a female)
	IIa	For patients with a normal QTc
Implantable cardioverter-defibrillator	I	For survivors of cardiac arrest
	IIa	For patients with syncope despite beta-blocker therapy
	IIb	For high-risk patients, including those with LQT2, LQT3 or who have a QTc lasting >500 ms

Table 3: Guidelines for the management of the Long-QT syndrome [5, 37]
* Levels of evidence:
I- conditions for which there is evidence or general agreement, or both, that a given procedure or treatment is beneficial, useful, and effective;

II- conditions for which there is conflicting evidence or divergence of opinion, or both, about the usefulness and efficacy of a procedure or treatment:

IIa- conditions for which the weight of evidence or opinion is in favour of usefulness and efficacy

IIb- conditions for which the usefulness and efficacy are less well established by evidence or opinion

THERAPEUTIC OPTIONS FOR CONGENITAL LONG-QT SYNDROME

The lack of data from large randomized control trials makes decision-making in the management of LQTS a challenge. Treatment options available to choose from include lifestyle modification, pharmacological therapy and surgery. In 2006, the major cardiology and electrophysiology societies in both Europe and America developed guidelines to aid physicians in their management of this syndrome (Table 3).

Lifestyle modification is universally considered essential for all patients whether symptomatic or not [37]. Recommendations include the avoidance of known triggers of cardiac events for the genotype in question and of all QT-prolonging drugs.

Beta-adrenoceptor antagonists remain the first-choice therapy for those with a prolonged QTc[28, 34, 37] as they prevent the acute rise of sympathetic activity that triggers most arrhythmias. Mixed opinions exist on the treatment of those with a normal QTc (Table 3).

Much research is currently underway into treatments targeted at specific genotypes. Although supported by experimental data, population studies confirming the efficacy of these treatments in protecting against arrhythmia are still lacking. At present, it might therefore be better to consider these as adjuncts to beta-blocker therapy rather than as a sole means of therapy [38].

Sodium channel blockers such as mexiletine have been proven to benefit patients with LQT3[27, 39] whereas flecainide was found to be useful for those with the D1790G mutation [40]. Flecainide is not, however, thought to be safe in treating those with other LQT3-mutations [41]. The therapeutic effects of L-type calcium channel blockers are also of current interest. They not only show promise for treating LQT8 and its associated gain-of-function mutations in cardiac calcium channels, but also for treating LQT3 as they additionally inhibit cardiac sodium channels [27, 38]. Experimental data also supports the use of oral potassium supplements, potassium-sparing agents, potassium channel openers and HERG (human *Ether-à-go-go* Related Gene) current enhancers in treating LQTS subtypes associated with reduced outward potassium current. Finally, gap junction coupling enhancers and the correction of protein trafficking defects are other therapeutic strategies under investigation.

Surgical options for the treatment of LQTS are considered in certain situations and include left cardiac sympathetic denervation (LCSD) and implantable cardiac defibrillator (ICD) insertion. The correct use of ICDs in LQTS is a heated topic. On one hand, they can reduce the risk of fatal arrhythmias in high risk patients [28]. On the other, they have a considerable effect on quality of life, particularly that of younger patients who require more battery and leads replacements. Additionally, their associated side effect of electrical storm caused by repeated electrical shocks has led to a substantial incidence of attempted suicide in adolescents [42]. Current guidelines strongly support their use in survivors of cardiac arrest, in conjunction with pharmacological therapy [35]. To a lesser degree, they are also recommend for other high-risk patients, including those with LQT2, LQT3, or a QTc >500 ms (Table 3). LCSD involves the removal of the first four thoracic ganglia which, like beta-blockers, reduces the rise in sympathetic tone that initiates arrhythmias. It should be considered where syncope is recurrent despite full-dose beta-blockade [28, 43]. It can also be used in conjunction with an ICD where beta-blockers are contraindicated and can dramatically reduce the frequency of ICD shocks and electrical storms in this instance [8, 28].

PROGNOSIS

The prognosis for patients with LQTS is dependent on a large number of factors including the syndrome subtype, the associated genetic mutation, the inheritance pattern, the degree of penetrance and whether or not the syndrome is recognised and treated. Most mutation carriers never experience symptoms [28]. As previously indicated, the majority of individuals that suffer a TdP arrhythmia usually recover. Approximately 13% of untreated patients suffer a cardiac arrest or SCD [44]. However, the prognosis for those who receive prophylactic therapy is usually good [28].

CONCLUSION

LQTS is a life-threatening disorder of the cardiac conduction system. It can be inherited or acquired and results in prolonged ventricular repolarisation which predisposes to fatal arrhythmias. In the past two decades, research has greatly advanced our understanding of the genetic, molecular and clinical aspects of LQTS. However, there still remain many shortcomings in our knowledge. Efforts must continue to unravel the genetics underlying this disorder and to improve the efficacy of prophylactic therapy.

In relation to disorders causing SCD overall, the ultimate goals of research include the development of automated screening which can definitively diagnose genetic predisposition to SCD, and of universal guidelines for the management of each disorder. This would hopefully lead to the enhanced recognition and treatment of those at risk and reduce the number of lives cut short.

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