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MOLECULAR ASPECTS OF LONG QT SYNDROME

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ABSTRACT

Congenital long QT syndrome (LQTs) is a hereditary, heterogeneous group of cardiac diseases characterised by a prolongation of the QT interval. Disease prevalence is 1 in 2,500 live births. The two cardinal manifestations of LQTs are syncopal episodes and electrocardiographic abnormalities (including prolongation of the QT interval and T wave abnormalities) that may cause sudden cardiac arrest and death. At molecular level, mutations in 15 distinct LQTS susceptibility genes encoding ion channel pore forming α–subunits have been implicated in its pathogenesis. Mutations in genes (*KCNQ1*, *KCNH2*, *KCNE1*, *KCNE2*, *CACNA1C*, *CAV3*, *SCN5A* and *SCN4B*) cause the disease by prolonging the duration of the action potential. More than 70 drugs currently available in the market can cause drug-induced long QT syndrome (LQTS) which is associated with *torsades de pointes* arrhythmias, causing sudden cardiac death. These drugs block the human Ether-à-gogo Related Gene (hERG) channel involved in the repolarization phase of the cardiac action potential, and thus lengthen the QT interval. Treatment should always be started with β-blockers. Treatment of drug-induced LQTS includes identifying and withdrawing the culprit drugs(s), infusing magnesium and, in resistant cases, acceleration of the heart rate.

KEYWORDS: Long QT syndrome, QT interval, genes, mutations, drugs.

INTRODUCTION

The long QT syndrome (LQTS) is a rare but important clinical disorder[1] characterized by abnormally prolonged ventricular repolarization and a high incidence of malignant

ventricular tachyarrhythmias, occur mainly during the physical or emotional stress.[2] Since 1975 it is included under the name of "Long QT syndrome". Two hereditary variants first one is associated with deafness and second one is not; they are referred to as the Jervell and Lange-Nielsen syndrome (J-LN) and as the Romano-Ward syndrome (R-W), respectively. Long-QT syndrome has been subdivided into many types based on the gene in which the causative mutations occur. The most prevalent forms of LQTS are LQT1 and LQT2 (due to mutations in potassium channels), and LQT3 (due to a sodium channel mutation).[1] It affects commonly to children and young adults with frequent faints or even sudden death. The most common form of LQTS is inherited as a dominant pattern, which shows that each of the children of an affected parent has a 50% chance of inheriting this disorder.

Every heart beat is triggered by electrical signal which tells the heart's muscle cells to contract. After contracting, the cells must recover or relax before another heart beat is initiated. The amount of time period needed by these cells to recover can be measured on an ECG and this is called the QT interval. If the next electrical signal arrives before the muscle cells have completed the recovery period a dangerously fast heart rate can occur leading to a decrease in blood pressure and loss of consciousness.[3] In most reported cases, death was caused by the malignant polymorphic ventricular arrhythmia called torsades de pointes (TdP). Congenital as well as acquired forms of LQTS are known. Administration of drugs is one of the most frequent causes of acquired LQTS. Drug-induced long QT syndrome can, thus, be defined as an "iatrogenic" form of potentially lethal condition. Cardiologists are familiar with this adverse drug effect because it has become a well-known complication of anti arrhythmic drug treatment.[4]

EPIDEMIOLOGY

Inherited LQTS is estimated to affect between one in 10,000 people[5]

CLASSIFICATION

It can be classified as congenital as well as acquired typed.

Congenital

The condition is inherited as a monogenic disorder with primarily autosomal dominant inheritance and variable penetrance. Multiple genetic mutations within at least 13 genes have been identified as the cause of LQTS.

- LQT1 is due to mutations within the KCNQ1 gene.

- LQT2 is due to mutations within the KCNH2 gene.
- LQT3 is due to mutations within the SCN5A gene.
- LQT4 to LQT13 have been described but are responsible for only <10% of cases.

Inherited as either an autosomal dominant or a recessive trait, the LQTS can be phenotypically categorised into three congenital syndromes.

- Romano-Ward syndrome is inherited as an autosomal dominant trait which may result from a mutation in any one of 13 identified genes and is not associated with deafness.
- Jervell and Lange-Nielsen syndrome is inherited as an autosomal recessive trait that results from a homozygous mutation in KCNQ1and is clinically characterised by a very severe form of LQTS and sensorineural deafness,and the affected individual may experience their first cardiac event during infancy period.
- Andersen-Tawil syndrome, also known as hypokalaemic periodic paralysis or LQT7, is a rare autosomal dominant condition and the affected patients of which has periodic paralysis and ventricular tachyarrhythmias, and have a variety of dysmorphic features.

Acquired

Several factors are associated with the development of a prolonged QT interval:

- Drugs
- Electrolyte imbalances
- Bradyarrhythmias
- CNS lesions
- Malnutrition[6]

MOLECULAR GENETICS OF LQTS

Long QT syndrome is an inherited disease. The most significant breakthrough occurred in 1991, when Keating illustrated the tight linkage between LQTS and the Harvey RAS1 gene locus on the short arm of chromosome 11 (LQT1) which was followed by the finding that other LQTS families were linked to chromosomes 3 (LQT3) and 7 (LQT2) and by a report that linkage to chromosome 4 was also present in LQTS. Based on the clinical evidence that LQTS is an electrical disease, genes encoding ion channel proteins have been considered candidate genes for the disease. The gene for LQT2 is *HERG*, which is a potassium channel conducting Ikr current and the gene for LQT3 is *SCN5A*, which is the cardiac sodium channel gene. The gene for LQT1 is *KvLQT1*, which is a component of the potassium channel

conducting the Iks current. Recently, another two LQTS genes have been identified on chromosome 21: *KCNE1* or *minK*, the gene for LQT5; and *KCNE2* or *MiRP*, the gene for LQT6. The gene for LQT4 on chromosome 4 has not been yet identified.

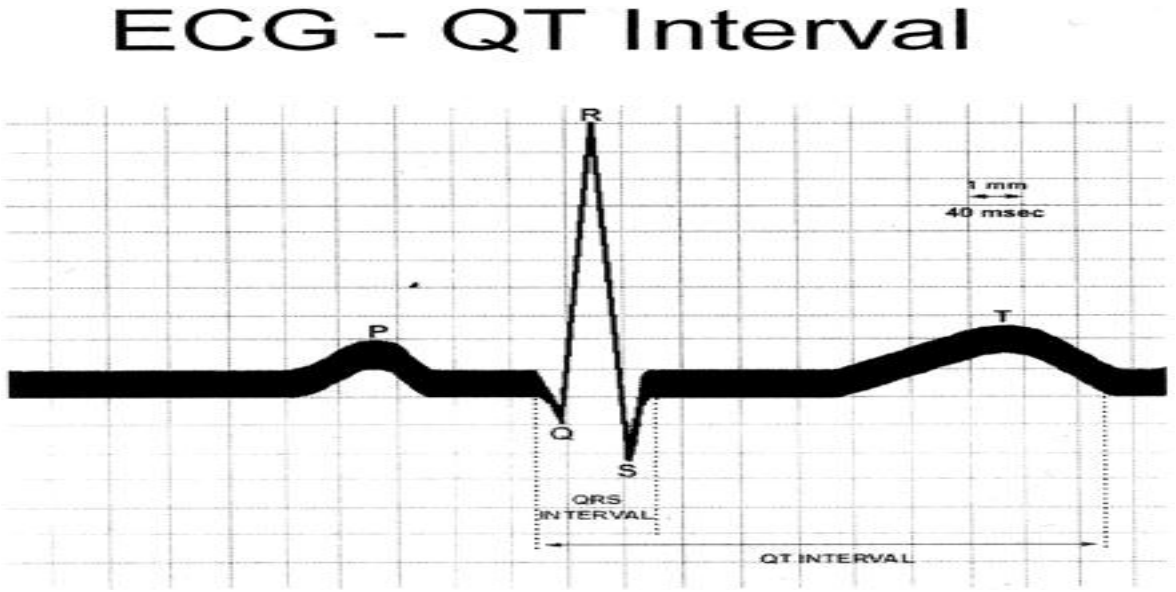
The relative distribution of mutations between the known genes suggests that *KvLQT1* accounts for 54% of the mutations that has been identified followed by *HERG* 35% and *SCN5A* 10%. *KCNE1* and *KCNE2* are very rare causes of LQTS.[2]

NORMAL VALUES OF QT INTERVAL

The QT interval is measured from the onset of QRS complex to the end of the T wave. Small physiological U waves should not be included in the measurements of the QT interval. However, tall U waves that are not separated from the T wave should be considered pathological and may be counted as a part of the QT interval. The QT interval adapts to the heart rate as, the higher the rate, the shorter the QT interval. That is why it is accepted to normalise the QT interval for the heart rate. Despite several limitations, the most commonly used formula to correct the QT interval value (QTc) for the heart rate is the Bazett formula, where QTc =QT/(RR)1/2[7], RR is the preceding RR duration written in seconds; which makes QTc equal to QT for a heart rate of 60 bpm. For yet unknown reasons, adult females have on average a QTc interval of about 20 ms longer than that of adult males, and in consequence one has to refer to different normal values for both genders.[8] Table shown below presents QTc values (corrected with the Bazett formula) that are considered normal, borderline and clearly prolonged for both the genders. Normal values of qt interval are given in table no 1.[9]

Table 1: Normal values of qt interval

	Adult Males	Adult Females
Normal	<430 ms	<450 ms
Borderline	431–450	451–470
Prolonged	>450	>470



DIAGNOSIS

The diagnosis is done in two phases as clinical diagnosis and molecular diagnosis.

Clinical diagnosis

To overcome the difficulties, diagnostic criteria were first proposed in 1985 and were subsequently updated in 1993 and then again in 2006. The new diagnostic criteria are listed in table below.

		Points
ELECTROCARDIOGRAPHIC FINDINGS #		
A QTc^	> 480 ms	3
	460 – 470 ms	2
	450 – 459 (male) ms	1
B TORSADE DE POINTES *		2
C TORSADE DE POINTES *		1
D NOTCHED T WAVE IN 3 LEADS		1
E LOW HEART RATE FOR AGE @		0.5
CLINICAL HISTORY		
A SYNCOPE *	WITH STRESS	2
	WITHOUT STRESS	1
B CONGENITAL DEAFNESS		0.5
FAMILY HISTORY $		
A FAMILY MEMBERS WITH DEFINITE LQTS		1
B UNEXPLAINED SUDDEN CARDIAC DEATH BELOW AGE 30 AMONG IMMEDIATE FAMILY MEMBERS		0.5

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

^ QTc calculated by Bazett's formula where QTc = QT/√RR

* Mutually exclusive

@ Resting heart rate below the 2nd percentile for age

$ The same family member cannot be counted in A and B.

SCORE: ≤ 1 point = low probability of LQTS

> 1 to 3 points = intermediate probability of LQTS

≥ 3.5 points = high probability of LQTS[10]

Molecular diagnosis

Molecular diagnosis should always be attempted in families or individuals to whom the diagnosis of LQTS has either been made or is predicted on sound clinical grounds. When molecular diagnosis is successful (70–80% of cases in laboratory), it conclusively establish the disease state in clinically borderline individuals and especially in apparently unaffected individuals.[10]

Data from the International Registry on 246 gene carriers (112 LQT1, 72 LQT2 and 62 LQT3) showed that LQT1 & LQT2 gene carriers are at higher risk of becoming symptomatic and also have a higher number of cardiac events than LQT3 gene carriers. [11]

TREATMENT

The trigger for life-threatening arrhythmias of LQTS is represented by a sudden increase in sympathetic activity, largely mediated by the quantitatively dominant left cardiac sympathetic nerves.[10] The choice of treatment is based on the presence or absence of symptoms, as well as on the types of symptoms and the degree of sudden death in family members.

Beta-adrenergic blockade

Beta-adrenergic blocking drugs are considered to be the important treatments of choice in symptomatic LQTS patients.[11] Propranolol is still the most commonly used drug of choice, at a daily dosage of 2 to 3 mg/kg with the main advantages of propranolol being its lipophilicity which allows it to cross the blood-brain barrier, and its well known tolerability for chronic therapy whereas nowadays nadolol is used more frequently, because of its longer half-life allowing twice a day administration, usually at 1 mg/kg/day. β-blockers rarely results

in excessive bradycardia, if the dosage is very gradually increased over several weeks. [14] In patients who cannot tolerate beta-blockers because of excessive bradycardia, and in patients in to whom this therapy may have limited usefulness as they tend to have TdP at low heart rate, the combination of beta-blockers and cardiac pacing may be employed, or left cardiac sympathetic denervation is required.[11]

Left cardiac sympathetic denervation(LCSD)

Left cardiac sympathetic denervation requires removal of the first four to five thoracic ganglia following a small incision in the left subclavian region.[12] LCSD is formed by an extrapleural approach which makes thoracotomy unnecessary. The average time required for the complete operation is 35-40min. Left cardiac sympathetic denervation prevents lethal arrhythmias of LQTS, also reduces QT dispersion, which is a marker of electrical instability.[13] If the patient continues to have syncope despite full-dose beta-blockade, LCSD could be performed and ICD implants could be considered.

Cardiac pacing

Cardiac pacing is clearly indicated in LQTS patients with atrioventricular block.[14] In infants or young children with 2:1 AV block this remains a reasonable choice, as a bridge to the ICD.[15] Pacemakers should never be used as a sole therapy. In patients with pause dependent TdP, the combination of a pacemaker and beta-blockers is not the only choice. Left cardiac sympathetic denervation should also be considered as this selective denervation does not significantly reduce heart rate.

CONCLUSION

The sound data available, dictate the therapeutic approach towards the patients affected by LQTS who already had a syncopal episode. Treatment should always start with β-blockers. If the patient has one or more syncope despite full dose β-blockade, ICD implant should be considered with the final decision being based on the individual patient characteristics (age, sex, previous history, mutation-specific features, presence of ECG signs- including 24 –hour Holter recording indicating high electrical instability.

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