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Review Article

Review - Long Qt Syndrome.

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Short Title: Long Qt Syndrome

Abstract

This article reviews long QT syndrome, addressing congenital and acquired forms, diagnostic criteria, risk stratification, treatment with medications and implantable cardioverter-defibrillator, as well as the importance of family screening and physical activity management.

Keywords : *long QT syndrome, arrhythmias, cardiology, genetic testing, defibrillator, sports.*

INTRODUCTION

Congenital long QT syndrome (LQTS) is a hereditary genetic disorder that causes ventricular repolarization dysfunction, increasing the risk of malignant ventricular arrhythmias and sudden cardiac death (SCD). It presents incomplete penetrance and variable expressivity.

LQTS occurs due to disorders in ion channels, either by loss of function in potassium channels or gain of function in sodium or calcium channels, resulting in prolonged QT intervals.

Over time, the number of identified mutations has increased, and 17 genes have been identified to date.[1]

A study conducted by Peter J. Schwartz in 2009 estimated the prevalence of LQTS at approximately 1:2500 live births.[2]

The risk of SCD is less than 0.5% in untreated asymptomatic patients with LQTS.[3] If there is a history of syncope, this rate rises to 5%.[4]

The first descriptions involved an autosomal dominant inheritance pattern (Romano-Ward Syndrome) and an autosomal recessive inheritance pattern (Jervell-Lange-Nielsen Syndrome), the latter accompanied by congenital deafness.[5]

GENETICS

It is important to keep two genetic concepts in mind. Penetrance refers to whether an individual with an altered gene expresses the disease trait. In complete penetrance, all individuals will show the disease phenotype, while in incomplete penetrance, the individual may or may not exhibit the phenotypic expression. If the disease does not manifest, it is important to note that the individual carries the altered gene and can pass it on to offspring, who may or may not be affected.

The concept of expressivity refers to the characteristics shown by the individual. Some affected individuals may exhibit more or fewer traits related to the disease, which also influences its severity. Simply put, although not literally correct, a patient with the disease may present it as “mild, moderate, or severe.”

Only three genes have been identified with definitive evidence of causing typical LQTS (KCNQ1, KCNH2, SCN5A). Four other genes (CALM1, CALM2, CALM3, TRDN) have shown strong or definitive evidence for atypical LQTS. Nine genes (AKAP9, ANK2, CAV3, KCNE1, KCNE2, KCNJ2, KCNJ5, SCN4B, SNTA1) have been classified as having limited or disputed evidence as LQTS causative genes. These should not be routinely tested in the evaluation of patients and families with LQTS, and their request should only be considered for patients with a clinical presentation consistent with the specific phenotypic expression.[1]

CLINICAL AND EPIDEMIOLOGY

The suspicion of long QT syndrome arises from the clinical history, a 12-lead electrocardiogram (ECG), and family history. In young patients with syncope and/or cardiopulmonary

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arrest (CPA) without structural heart disease or reflex characteristics, the possibility of channelopathies, such as long QT syndrome, short QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, early repolarization syndrome, or idiopathic ventricular fibrillation, should always be investigated. Additionally, arrhythmogenic right ventricular dysplasia and hypertrophic cardiomyopathy should also be considered. Proper diagnosis and management can significantly impact the lives of these young patients and their families.

Symptoms such as recurrent syncope due to Torsades de Pointes can occur.[6] It is important to differentiate whether the syncope is of vasovagal origin, as treatment and prognosis differ.

There are also reports of LQTS patients, particularly type 2, presenting with epilepsy, as disturbances in potassium homeostasis in the hippocampus have been observed to result in epileptic activity.[7]

Other symptoms include palpitations, atrial arrhythmias, and sudden cardiac death. The increase in atrial arrhythmias is due to repolarization disturbances in the atria as well.[8]

A family history of SCD in a child or young person immediately raises the suspicion of LQTS, making it relevant to question cases of family members who drowned despite knowing how to swim or who were involved in car accidents under peculiar circumstances.

Symptoms typically begin around the age of 14.[9]

The most common triggers for type 1 include physical exertion, competitive sports, especially swimming, and emotional stress resulting from adrenergic stimuli. In type 2, events are more related to loud noises, alarm clocks, sudden scares, emotional stress, postpartum, and perimenopause. In type 3, similar to Brugada syndrome, events occur more often at rest or during sleep. It is important to note that a normal corrected QT interval (QTc) does not exclude the syndrome. Diagnosis can still be made with a normal QTc. Additionally, the dynamic nature of the syndrome must be understood, which is common in channelopathies, with variations in the QT interval throughout the day, over hours, or even beat-to-beat. It is possible to have a normal QT on one day and an abnormal one on another. In borderline cases, repeating ECGs over several days may be helpful.[10]

QT INTERVAL MEASUREMENT

Accurate measurement of the QT interval is crucial in the diagnosis of LQTS. The interval should preferably be measured in lead D2 or V5, and if these leads are unavailable due to artifacts or other reasons, adjacent leads should be used. The tangent method is employed to measure the end of the T wave, defined as the point where the tangent line to the steepest portion of the terminal arm of the T wave intersects the isoelectric baseline. The U wave should be excluded from the QT interval analysis.[10]

DIAGNOSIS

The diagnosis is established when there is a QTc ≥ 480 ms on repeated 12-lead ECGs, with or without symptoms, or when the long QT syndrome (LQTS) diagnostic score is greater than 3. It is also recommended to diagnose LQTS in the presence of a pathogenic mutation, regardless of the QT interval duration. Additionally, a QTc ≥ 460 ms on repeated 12-lead ECGs in patients with arrhythmic syncope, in the absence of secondary causes, is considered diagnostic.[11-12]

A patient may be diagnosed with long QT syndrome even in the presence of a normal or borderline QT interval. These patients are referred to as silent mutation carriers and account for approximately 36% of LQTS1 patients, 19% of LQTS2 patients, and 10% of LQTS3 patients.[7]

ADDITIONAL METHODS

Provocative tests, such as the exercise stress test, can help reveal LQTS in patients with a normal QTc at rest or aid in the suspicion of the specific LQTS type.

Currently, epinephrine challenge tests are no longer recommended for establishing the diagnosis, as they are considered Class III by the European cardiology guidelines.[9]

Electrophysiological studies are also not recommended in LQTS, being equally classified as Class III indication.[9]

Exercise Stress Test

The exercise stress test, in addition to aiding in diagnosis, can also help distinguish between LQTS1 and LQTS2 patients. Both may present QT interval prolongation during the recovery period. LQTS1 patients show a gradual decrease in QTc during recovery, while LQTS2 patients exhibit a progressive increase in QTc intervals as the recovery period progresses.[14]

A QTc increase of more than 30 ms (recovery QTc − baseline QTc) can also help identify patients with LQTS, particularly LQTS1, even when the resting QTc is within normal limits.

Schwartz, after evaluating studies, included this criterion in his algorithm, suggesting that a cutoff of 480 ms in the 4th minute of recovery would assist in diagnosing probands. This parameter would not be useful for LQTS3 patients, only for types 1 and 2.[15]

A simple maneuver can be performed based on the response of the QT interval to a brief acceleration in heart rate provoked by standing. The ECG should be performed with the patient in a supine position after resting and then again immediately after standing up. In a study, this maneuver showed that the QT interval in controls was reduced by 21 ± 19 milliseconds, while the QT interval in LQTS patients increased by 4 ± 34

milliseconds (P < 0.001). Additionally, the test may expose abnormal T waves. A phenomenon called "QT stunning" may occur, where QTc prolongation can persist even after heart rate returns to baseline. This maneuver was not very useful in LQTS2 patients.[16-17]

24-Hour holter

The 24-hour Holter can assist in evaluating the presence of polymorphic ventricular arrhythmias, such as asymptomatic Torsades de Pointes, in addition to allowing the analysis of multiple QTc measurements at different times of the day. It is also possible to assess whether the mechanism of a potential Torsades began following a pause.

Genetic testing

Genetic testing helps with diagnosis and risk stratification, although it is not easily accessible in most locations.

A genetic panel covering most of the related genes can be requested, or genetic testing can be targeted toward the three main genotypes (KCNQ1, KCNH2, and SCN5A). These three genes account for 90% of positively genotyped cases.[18] Genetic screening identifies the mutation in 75% of LQTS cases.[9]

Caution is required when ordering genetic testing, as appropriate use can help prevent sudden death, while inappropriate use may cause harm to the patient, such as anxiety, lifestyle changes, professional interference, or even the unnecessary implantation of an implantable cardioverter-defibrillator (ICD).

Specific testing for the mutation found in the index case is recommended for the patient's parents, siblings, and children. Genetic testing in relatives is indicated even in the presence of a negative clinical phenotype and ECG, as a normal QT interval is not sufficient to rule out the syndrome. If the genetic test, history, and 12-lead ECG are all negative, LQTS is ruled out.

Risk stratification

Risk stratification for LQTS patients aims to identify those at higher risk of cardiac arrest or sudden cardiac death.

Genetic testing in the case of LQTS, unlike some other channelopathies, aids in risk stratification, as type 3 presents a higher risk than type 2, which in turn presents a higher risk than type 1. Jervell and Lange-Nielsen syndrome (autosomal recessive) and Timothy syndrome (LQTS8) are associated with high risk and tend to respond poorly to therapies.

A family history of sudden death in young individuals, while helpful for diagnosis, is not used for risk stratification because the syndrome shows variable penetrance and expressivity.

In LQT1, the transmembrane location of the mutation is an independent risk factor for cardiac events, while in LQT2 patients, mutations in the pore region are associated with a higher risk.[1]

A QTc measurement over 500 milliseconds, as well as the presence of T-wave alternans, are also considered high-risk factors. Studies have shown and suggested sex differences, though not fully solidified. It is believed that life-threatening events were more frequent among women with LQT2 than men with LQT2, and more common in men with LQT3 than women with LQT3.[3]

Other high-risk predictors include the occurrence of arrhythmic events despite optimized medical therapy. Women are at increased risk of arrhythmias during pregnancy and in the first year postpartum, particularly in type 2 cases.[9]

TREATMENT

General recommendations

Drugs that prolong the QT interval should be avoided, and a list of such drugs can be consulted at the website *crediblemeds*.org. Electrolyte disturbances should be prevented and promptly corrected if they occur. It is important to avoid genotype-specific triggers, such as avoiding adrenergic stimuli, particularly in LQTS type 1, and avoiding the use of alarm clocks in LQTS type 2.

LQT2 patients are more susceptible to arrhythmic events when serum potassium levels drop. Oral potassium supplements or the use of potassium-sparing agents, such as spironolactone, may be recommended. There is evidence that grapefruit juice prolongs the QT interval in healthy volunteers and LQTS patients, suggesting a potential role as a "pro-arrhythmic food."

Medications

Beta-blockers are the first-line treatment, with non-selective ones such as nadolol or propranolol being the most recommended. They are indicated for all patients diagnosed with long QT syndrome with a prolonged QTc, as well as for patients with pathogenic mutations, even with a normal QTc.[9]

The dose of propranolol used is 2-4 mg/kg/day, while the dose of nadolol is 1-2 mg/kg/day, with nadolol having a longer half-life, allowing for once-daily dosing. Beta-blockers show a significantly better response in LQTS type 1, a less pronounced response in type 2, and an uncertain response in type 3.

This medication should be reserved for patients with LQTS type 3 with prolonged QT intervals. It belongs to class IB of the Vaughan-Williams antiarrhythmic classification and acts by blocking the late sodium current. There is no clear indication whether it should be administered alone or in combination with beta-blockers.[9]

Left cardiac sympathetic denervation

Left cardiac sympathetic denervation (LCSD) is also a treatment option. This procedure results in a reduction of more than 90% in cardiac events.[9]

Implantable cardioverter defibrillator (icd)

Patients with aborted sudden cardiac death (SCD) should receive an ICD, in addition to following general recommendations and using beta-blockers and mexiletine in the case of LQTS type 3. If the patient is undergoing treatment and develops arrhythmic syncope or intolerable ventricular arrhythmias, an ICD should also be indicated. In cases where medical therapy is contraindicated or not tolerated, denervation or ICD implantation may be performed. If the ICD is contraindicated, refused, or there are recurrent shocks, denervation should be performed.

There is also the possibility of calculating risk using the 5-year LQTS risk calculator and basing the ICD indication on this calculation, although this recommendation is considered weaker.[9]

Sports And Long Qt Syndrome

A few years ago, LQTS patients were advised not to participate in competitive sports. However, after studies with athletes and the absence of symptoms or events related to physical activity, this guidance has changed.

Currently, according to the American College of Cardiology, the athlete must be asymptomatic and on treatment for at least 3 months. The presence of an automatic external defibrillator (AED) is also required. However, aquatic sports are contraindicated for athletes with LQTS1.[19,20]

Regarding the European guidelines, athletes with LQTS and aborted sudden cardiac death (SCD) or arrhythmic syncope are still prohibited from participating in competitive sports. Patients with a positive ECG phenotype, even if asymptomatic and on beta-blockers, are also not considered eligible for competitive sports, although they may engage in recreational exercise of light to moderate intensity.[20]

The implantation of an ICD does not authorize participation in intensive or competitive sports. Participation in sports with an ICD is possible, provided specific recommendations are followed. If LQTS is acquired, sporting activity should be discontinued until the factors leading to the condition have been resolved.[20]

Acquired Long Qt Syndrome

The acquired form of the syndrome is much more common than the congenital type and is associated with the use of drugs that prolong the QT interval, electrolyte disturbances (hypokalemia, hypomagnesemia, hypocalcemia), bradycardia, and atrioventricular blocks. Several medications are related to QT interval prolongation. Patient factors, such as age, female sex (especially between puberty and menopause), cardiac comorbidities, and impaired repolarization reserve, may also contribute to the development of the acquired form.

Most medications act by reducing IKr currents. LQTS type 2 is most frequently unmasked by drug use.

Among antidepressants, tricyclics and citalopram cause greater QT interval prolongation compared to other selective serotonin reuptake inhibitors (SSRIs) and should therefore be avoided as first-line therapy in patients with heart disease or known risk factors for QT prolongation. Almost all antipsychotics have been documented to cause QT interval prolongation, but typical agents carry a higher risk than atypical ones. Opioids have also been associated with QT interval prolongation, with methadone being a potent blocker of the hERG potassium channel, causing QT prolongation in up to 37% of cases.

There is evidence of genetic predisposition in some individuals with acquired LQTS, and genetic testing in the context of drug-induced LQTS requires individualized consideration. Up to one-third of patients with acquired LQTS carry mutations in one of the major genes related to LQTS, with KCNH2 being the most common.

Family Members

In patients clinically diagnosed with long QT syndrome, genetic counseling and genetic testing should be performed.[9]

If a specific mutation is identified in the patient, first-degree relatives (parents, siblings, children) should also be referred for genetic counseling and specific mutation testing, even if asymptomatic.[9]

An ECG and exercise test (when feasible) should be performed on first-degree relatives from birth. If the phenotype is negative and no pathogenic variants are present, the family member can be discharged.[9]

CONCLUSION

Long QT syndrome can be either congenital or acquired. Distinguishing between them is important, as it influences treatment and prognosis. Genetic long QT syndrome (LQTS) poses a significant risk for severe ventricular arrhythmias and sudden death. Early diagnosis, based on clinical, genetic, and electrocardiographic data, is essential for identifying high-risk patients and implementing effective preventive strategies. Risk stratification, guided by genetic factors, QTc duration, and clinical history, allows for an individualized therapeutic approach, minimizing the risk of fatal events. Additionally, investigating first-degree relatives is essential.

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