Review article

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LONG-QT SYNDROME: MISDIAGNOSIS AND OVERDIAGNOSIS, CLINICAL SUSPICION AND THE APPROPRIATE MANAGEMENT

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Long-QT syndrome is a potentially lethal cardiac channelopathy that can be mistaken for palpitations, neurocardiogenic syncope, and epilepsy. Delayed diagnosis of long QT syndrome is frequent. Symptoms are often attributed to alternative diagnoses, most commonly seizure disorders. Long QT syndrome has significant mortality, which is reduced with appropriate management. We aim to underline the importance of clinical awareness and correct management to reduce the fatal cases of this syndrome.

Key words: Misinterpretation of symptoms ▪ Safe approach to LQTS

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Misdiagnosis and over-diagnosis

Long QT syndrome (LQTS) is a congenital disorder characterized by prolongation of the QT interval on the surface electrocardiogram and a propensity to ventricular tachyarrhythmias, which may lead to syncope, cardiac arrest, or sudden death in an individual with a structurally normal heart, and it is one of the main causes of sudden unexplained death in autopsy-negative cases.

The diagnosis of LQTS is not easy since 2.5% of the healthy population have a prolonged QT interval, and it has been estimated that more than 20% of LQTS patients have a normal QT interval (QTc<440 ms) (1). The incidence of congenital LQTS is difficult to determine. Previously it was considered to be 1:20,000, then 1:5,000, and currently it is considered to be at least 1:2,500 (2, 3, 4). The reason that the actual prevalence cannot be determined precisely results from the fact that a large number of cases are under diagnosed.

Misinterpretation of symptoms appears to be responsible for most of the diagnostic miscues, with 39% of patients experiencing delay between initial presentation and diagnosis. Part of the problem is that many patients are only children, in whom diagnosis of epilepsy seems far more likely than a heart condition (5). The primary referral is to the neurologist and a breakdown in communication still persists between the neurologist, the cardiologist and the patient's family (6, 7). If the patient is initially labeled as epileptic, the delay to diagnosis is more likely to be longer (8).

The technical difficulties in accurately measuring the QT interval and the methodological controversies that exist, are in part to blame (9, 10). Even in cases where ECG is requested, errors in interpreting the results are common. A New Zealand cohort observation, consistent with other recent work, suggests that less than 40% of non-cardiologists and fewer than 50% of cardiologists were able to calculate a QTc interval correctly (8).

On the other hand, new research suggests that up to 40% of patients diagnosed with LQTS do not actually have it and are receiving treatment unnecessarily with dramatic lifestyle changes (11). However, failure to diagnose it correctly is much more dangerous than over-diagnosis.

Mortality can be as high as 70% in patients who remain untreated over a 10 year period. Although sudden death usually occurs in symptomatic patients, it happens with the first episode of syncope in about 30% of the patients (2, 13). This emphasizes the importance of diagnosing LQTS in the presymptomatic period.

Clinical suspicion

Time of presentation - Patients with congenital LQTS usually come to medical attention in childhood, adolescence, or early adulthood.

They usually present with palpitations, syncope or near pre-syncope, seizures, or cardiac arrest. Syncopal episodes associated with secondary seizures may be misdiagnosed as primary seizure disorders. The seizures are likely to be secondary to hypoperfusion of the brain during arrhythmic events (6, 14, 15).

Cardiac dysrhythmias can be initiated by an external trigger, such as emotional stress, exercise, or sudden loud noises (i.e., an alarm clock or telephone). However, in patients with the LQT3 genotype, ventricular arrhythmia is commonly seen during sleep (9, 16).

The symptoms of LQTS occur only when the patient develops an episode of torsades de pointes (meaning torsion around a point), and the degree of symptoms depends on the length of time the arrhythmia persists. In this arrhythmia, the heart rhythm is extremely rapid, and the shape of the complexes on the ECG are constantly changing, often resembling a sine-wave pattern as in this picture. When the heart's electrical system behaves in this way, effective pumping is impossible. Symptoms are related to the duration of the arrhythmia. If it is short and momentarily, a few seconds of extreme dizziness may be the only symptom. If it persists for more than 10 seconds or so, syncope occurs. And if it lasts for more than a few minutes, the victim never regains consciousness (17).

Postmortem genetic testing studies for channelopathies have shown that even 20% of sudden unexplained death cases at autopsy in fact had LQTS as an underlying pathogenic cause (18).

Fortunately, many people with LQTS have a mild form, and never experience life-threatening symptoms (17).

In patients with suspected congenital LQTS, the initial evaluation should be directed at calculating the QTc interval on a resting ECG. For practical purposes, any value

over 0.45 seconds should be considered abnormal.

The QT interval should be corrected by Bazett's formula ($QTc=QT/\sqrt{RR}$. The QTc interval is the QT interval corrected for heart rate because, under normal physiological circumstances, the actual measured QT interval adjusts with the heart rate; in other words, it is longer at slower rates and shorter at faster rates. A QTc interval of more than 0.45 sec for adult males and 0.46 sec for adult females is considered probably abnormal. Values in the range of 0.43-0.45 sec for males and 0.45-0.46 sec for females are considered a grey zone.

This issue is especially important when the heart rate is <50 bpm or >120 bpm and when athletes or children have marked beat-to-beat variability of the R-R interval. In such cases, long recordings and several measurements are required. The longest QT interval is usually observed in the right precordial leads (2).

Other ECG features that help to establish the diagnosis of congenital LQTS include:

An abnormal T-wave morphology, including notched or biphasic T waves.

The presence of T-wave alternans, which is defined as the regular alternation in T wave amplitude or polarity.

An increased QT dispersion, which is defined as the variability in QT duration among different ECG leads (2, 15, 19).

A scoring system for the diagnosis of congenital LQTS was established in 1985 by Schwartz et al. and revised in 1993 and still serves as the best guide for clinicians today (13). It assesses ECG features, clinical history and family history, in combination, in order to establish the level of probability (low, intermediate, high) of LQTS, as ECG features alone are often not enough to establish a diagnosis.

A significant percentage of patients with LQTS present with normal QTc duration. For instance, it has been estimated that 10% of LQTS patients present with QTc=0.45 sec'(20); therefore, if suspicion is high, despite a normal ECG and in the absence of clinical and family history, Holter monitoring or stress testing may be helpful in unmasking the long QT.

Genetic testing for congenital LQTS is now available in specialized centers, however, the practical application of genetic testing is still limited because of the complexity and heterogeneity of congenital LQTS. More than 10 genes have been identified, with more than 600 mutations. Mutations in five of these genes account for about 70 to 75 percent of long QT syndrome cases, and cause the forms referred to as LQT1, LQT2, LQT3, LQT5 and LQT6 (14, 15, 21, 22, 23). In addition, as many as 25% of patients have novel mutations (9, 24); therefore, a negative test does not exclude the disease. Please note that once a mutation is identified in the proband, that is, in the first patient in the family that seeks medical assistance and undergoes genetic testing, the rest of the family is easily diagnosed, since the the mutation is known. If a patient undergoes genetic testing and it is positive, then it is almost imperative for the rest of the family to be screened (25).

The specific genotype influences the clinical course, the kinds of triggering events that may initiate arrhythmias, the prognosis, and even the recommended form of treatment.

Management of LQTS

All patients with LQTS should avoid drugs that prolong the QT interval or reduce their serum potassium or magnesium levels. Potassium and magnesium deficiency should be corrected (14, 15, 26). All patients with congenital LQTS should be treated regardless of the presence of symptoms with conventional therapy (beta-blocker), because sudden cardiac death may be the first manifestation

of LQTS (27). Beta-blockers are the drugs of choice for patients with LQTS (9). The protective effect of beta-blockers is related to their adrenergic blockade that diminishes the risk of cardiac arrhythmias. Propranolol and nadolol are the beta-blockers most frequently used, though atenolol and metoprolol are also prescribed in patients with LQTS (2). Beta-blockers are effective in preventing cardiac events in approximately 70% of patients, whereas cardiac events continue to occur despite beta-blocker therapy in the remaining 30% (16, 26). (The actual numbers largely depend on the genotype –it differs between LQT1, LQT2 and LQT3 types- and also according to whether the patient was symptomatic or not before the initiation of treatment).

Although for years the recommended dosage of beta-blockers was relatively large (e.g., propranolol 3 mg/kg/d, or 210 mg/d in a 70-kg individual), recent data suggest that dosages lower than this have a protective effect similar to that of large dosages (2). Mexiletine (a sodium channel blocker) may improve protection in patients with LQT3. Some experts suggest the use of a beta-blocker combined with mexiletine in these patients (9, 14). An implantable cardioverter-defibrillator (ICD) has been shown to be highly effective to prevent sudden cardiac death (SCD) in high-risk patients (patients with aborted cardiac arrest or recurrent cardiac events (e.g., syncope or torsade de pointes) despite conventional therapy (i.e., beta-blocker alone). (9, 14, 16, 23, 28). Early ICD therapy should be considered in high-risk patients with Jervell and Lange-Nielsen syndrome, because the efficacy of beta-blockers has been found to be more limited in these patients (13).

Left cervicothoracic stellectomy is another antiadrenergic therapeutic measure used in high-risk patients with LQTS, especially in those with recurrent cardiac events despite beta-blocker therapy (more effective in patients with LQT1 than those with other types of LQTS). Cervico-thoracic stellectomy may be indicated in some high-risk patients and in patients who have had several ICD discharges while being treated with beta-blockade and an ICD (16). With this procedure the sympathetic denervation of the heart is achieved. This technique decreases the risk of cardiac events, but it does not completely eliminate it (24, 28). Therefore, ICD is superior therapy to cervico-thoracic stellectomy.

Gene-specific therapy is a promising area under investigation. Lifestyle modifications, including avoiding triggering factors, should be avoided. Physical activity, swimming, and stress-related emotions frequently trigger cardiac events in patients with LQTS. Therefore, patients should be discouraged from participating in competitive sports (9, 16). This recommendation is most important for patients with LQT1 or LQT2. Medications that prolong the QT interval should be avoided completely.

Conclusions

LQTS can be difficult to diagnose. Miscalculation of the QTc, misinterpretation of the normal distribution of QTc values and misinterpretation of symptoms appear to be responsible for most diagnosis miscues. Given the preventable mortality of LQTS, physicians investigating syncope and seizure should maintain a high index of awareness and suspicion. Failure to suspect or diagnose can lead to the potential irreparable outcome of sudden cardiac death. Failure to diagnose is much more dangerous than over-diagnosis. The mortality rate of LQTS can be significantly reduced with appropriate management.

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