The heterogeneous spectrum of the long QT syndrome

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Abstract

The long QT syndrome affects predominantly younger people who demonstrate structurally normal hearts. The underlying defect in the long QT syndrome seems to be genetic mutations in the cardiac ionic channels responsible for generating action potentials. Genetic linkage mapping has identified six genes (designated LQT1–6) associated with the Romano–Ward syndrome; two of these genes (LQT1, LQT5) are associated with the Jervell and Lange-Nielsen syndrome. All of these genes encode potassium channels with the exception of LQT3, which encodes a sodium channel. Mutations affecting these channels will lead to a derangement in ionic flows across the cytoplasmic membranes of cardiac cells, thereby leading to prolongation of the cardiac action potential and lengthening of the QT interval on the surface electrocardiogram. Long QT syndrome is a cause of death in young, otherwise healthy individuals.

The heterogeneity of the long QT syndrome also makes prognosis and risk stratification difficult. In patients with long QT syndrome genotypes 1 and 2, as well as during slower heart rates, men exhibited shorter mean QTc interval durations than did women; thus, women possess a predilection for developing torsades de pointes. In female probands with the congenital long QT syndrome, the postpartum period appears to confer a significant risk for experiencing a cardiac event. The study determined that certain combinations, such as exhibiting a QTc of 500ms or more, along with the presence of LQT1, LQT2, and LQT3 (with male gender), conferred a 50% or greater risk of a first cardiac event. Based on the observation that physical exertion and emotional stress are significant triggers for cardiac events in the setting of congenital long QT syndrome (specifically the LQT1 and LQT2 genotypes), avoidance of competitive sports seems to be a prudent lifestyle modification. The triggering events, prognosis, and risk stratification of the patient with long QT syndrome appear to be influenced by the underlying genotype. The primary treatment of congenital long QT syndrome, i.e., beta-blockade therapy with internal cardioverter defibrillator therapy, appears to be useful in a subset of patients.

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1. Introduction

The long QT syndrome is an uncommon condition characterized by a prolongation of the QT interval on the scalar electrocardiogram. This abnormal prolongation of the ventricular repolarization phase predisposes a patient to the development of ventricular tachyarrhythmias that are often precipitated by hyperadrenergic states [1]. Three major forms have been characterized thus far. One form has an autosomal dominant mode of genetic transmission and expresses a pure cardiac phenotype (Romano–Ward syndrome) [2,3]. The second has an autosomal recessive transmission and expresses congenital neuronal deafness (Jervell and Lange–Nielson syndrome) [4]. The third form is acquired – not inherited – and is caused by electrolyte disturbances or exposure to specific drugs.

The long QT syndrome affects predominantly younger people who demonstrate structurally normal hearts. The prolonged QT interval leads to electrical instability, which can eventually culminate in ventricular tachycardia or torsades de pointes [5]. Recent studies have shed light on this elusive condition, which can have fatal repercussions.

2. Pathogenetic mechanisms

The underlying defect in the long QT syndrome seems to be genetic mutations in the cardiac ionic channels responsible for generating action potentials. Genetic linkage mapping has identified six genes (designated LQT1–6) associated with the Romano–Ward syndrome; two of these genes (LQT1, LQT5) are associated with the Jervell and Lange-Nielsen syndrome [6]. All of these genes encode potassium channels, with the exception of LQT3, which encodes a sodium channel [7]. Mutations affecting these channels will lead to a derangement in ionic flows across the cytoplasmic membranes of cardiac cells, thereby leading to prolongation of the cardiac action potential and lengthening of the QT interval on the surface electrocardiogram. The potassium channels carrying the I_Kr and I_Ks currents of the cardiac action potential are multimeric in structure. Alleles from both parents are thought to contribute to the construction of these potassium channels. A mutant allele from a single parent will lead to a “loss of function”; the total current conveyed by the defective potassium channel will be reduced. In contrast, a mutation in the sodium channel carrying the I_Na current will lead to a “gain in function”; the sodium channel will remain persistently activated beyond physiologic normalcy [1].

The heterogeneity of mutations in the genotypic substrate leads to a variety of phenotypic expressions in the long QT syndrome. For example, patients exhibiting a LQT1 gene mutation are more susceptible to syncopal events and malignant dysrhythmias in the presence of adrenergic stimulation. Such stimulation can be due to physical exercise (diving and swimming seem to be exclusive triggers) as well as to emotional stress [8–10]. The LQT1 gene encodes a potassium channel whose predominant current is I_Ks. This specific current is also predominant during periods of increased sympathetic activation. A reduced I_Ks stemming from a defective ionic channel can lead to inadequate action potential shortening during states of adrenergic stress, thereby accounting for a high prevalence of dysrhythmic events during physical exertion [1]. In contrast, a mutation in the LQT3 gene appears to be associated with sudden cardiac death transpiring during the sleep state [11]. The postulated mechanism involves a defective inactivation of the I_Na, the current responsible for depolarization or Phase 0 of the cardiac action potential. The persistent activated state will result in an increase in the plateau inward sodium current [1]. Moreover, bradycardia occurring during the sleep state may excessively prolong the QT interval, thereby increasing the likelihood of a fatal ventricular dysrhythmia occurring [12]. This dichotomy between triggering events, which exists for LQT1 and LQT3, does not seem to hold true for LQT2. Patients with the LQT2 mutation seem to experience events during states of physical exertion as well as rest [25]. However, events provoked by auditory stimuli (e.g., ringing emanating from an alarm clock or a telephone) seem to transpire almost exclusively in patients with the LQT2 mutation [9,25–28].

3. Diagnostic and prognostic considerations

Elucidation of the genetic causes of the long QT syndrome has afforded an excellent potential to enhance the diagnostic reliability of this often unrecognized entity. Long QT syndrome is a cause of death in young, otherwise healthy individuals. Young athletes involved in competitive sports are also affected. Since long QT syndrome is not associated with any aberrant anatomic cardiac markers identifiable during life or at autopsy, its role in inducing premature death has probably been underestimated. Diagnosis is easy to establish when the QTc interval is markedly prolonged (e.g., ≥0.50s). However, often the QTc interval is only moderately prolonged, and this has led to the imprecise nature of phenotypic electrocardiographic diagnosis [8,13]. Within the long QT syndrome pedigrees, a broad range of QTc interval measurements exists among individual family members stemming from gene mutations. For example, approximately 40% of carriers with mutations in chromosomes 7 and 11 exhibit QTc interval values (0.41–0.47s) that overlap with QTc interval values observed in non-carriers. Moreover, between 5% and 15% of all carriers exhibit false-negative QTc interval values of 0.44s or below [8]. In view of such variation, it seems reasonable to conclude that measurement of the QTc interval is neither completely sensitive nor specific for establishing the presence of long QT syndrome [14]. In order to sharpen diagnostic reliability, an elaborate point score system has been formulated, which takes into account other features of
the long QT syndrome (e.g., torsades de pointes, T-wave alternans, syncope, congenital deafness, and family history) [13]. A statement approved by the American Heart Association advocates the use of molecular diagnosis when evaluating relatives within long QT syndrome families [14]. Carriers of gene mutations who exhibit false-negative or ambiguous phenotypic diagnoses are still at risk of experiencing clinical events.

The heterogeneity of the long QT syndrome also makes prognosis and risk stratification difficult. According to the results of three major epidemiological studies, certain characteristics appear to increase the likelihood of a syncopal event or sudden cardiac death occurring in probands (index cases) who are diagnosed with long QT syndrome. These characteristics include the following: congenital deafness, history of syncope, documented history of ventricular arrhythmias, family history of sudden cardiac death, female gender, a QTc length exceeding 0.60s, and medical noncompliance after an event [15–17]. The increased tendency for adult women to experience cardiac events is noteworthy. In patients with long QT syndrome genotypes 1 and 2 as well as during slower heart rates, men have exhibited shorter mean QTc interval durations than women; thus, women possess a predilection for developing torsades de pointes [18]. When compared with men, women exhibit a longer QTc interval duration as well as a greater response to drugs that block the \( I_{Kr} \) current, the rapid component of the delayed rectifier potassium current which is involved in establishing ventricular repolarization. Both of these factors appear to facilitate the development of torsades de pointes in women. The presence of a longer QTc interval and a greater response to \( I_{Kr} \)-blocking drugs (e.g., dofetilide) in women is very likely due to the effect of sex steroids. These sex steroids appear to modulate the regulation of ionic channel expression. For example, estrogen potentiates QT interval prolongation induced by bradycardia, thereby increasing the development of arrhythmia. In contrast, androgens like testosterone shorten the QT interval, thereby conferring a protective benefit when the individual is exposed to \( I_{Kr} \)-blocking agents like dofetilide. Evidence has also been gleaned that implicates extragonadal factors in explaining the discrepancies of ventricular repolarization between the genders [22,56,57]. In female probands with the congenital long QT syndrome, the postpartum period appears to confer a significant risk of experiencing a cardiac event. According to one study, approximately 10% of probands experienced the first cardiac event during the postpartum phase [20]. Causal mechanisms postulated to explain this increased risk include heightened sympathetic activity and increased levels of estrogen and progesterone, which may influence the number and function of mutant ion channel proteins [16,21–23]. In view of the above findings, it would be interesting to examine the effects of oral contraceptive pills on QT interval durations. These oral agents are in widespread use among younger women and modulate the hormonal milieu. A specific study addressing this question does not appear to have been conducted based on a recent survey of the medical literature. Evidence from oophorectomized rabbits indicates that estrogen replacement can excessively prolong the ventricular repolarization phase as well as increase the incidence of early after depolarizations in the setting of \( I_{Kr} \)-blockade [58]. Both of these phenomena are proarrhythmic. The issue of whether such observations translates into a causal relationship of chronic estrogen exposure leading to an increased risk of drug-induced torsades de pointes still needs to be rigorously investigated.

In addition to the phenotypic characteristics outlined above, genotype appears to affect the natural history of long QT syndrome and, thus, has an important role in determining prognosis. A recently published study from Italy examined the effects of genetic locus on the clinical course of long QT syndrome, along with the interplay existing between locus and phenotypic variables like gender and duration of repolarization (QTc). The study determined that certain combinations, such as exhibiting a QTc of 500ms or more, along with the presence of LQT1, LQT2, and LQT3 (with male gender), conferred a 50% or greater risk of a first cardiac event. Specifically, a first cardiac event was defined as syncope, cardiac arrest, or sudden death occurring before the age of 40 years or prior to the initiation of therapy. Combinations of variables that conferred a risk of 30% or less of experiencing a first cardiac event included the following: a QTc below 500ms in the presence of LQT2 locus (with male gender) and LQT1. Thus, the heterogeneity of the long QT syndrome disease spectrum also seems to translate into differential risk stratification. The authors of this study also concluded that prophylactic beta-blockade therapy is warranted in those individuals falling into the intermediate and high risk categories of the risk stratification scheme [19]. As further investigation into this disease spectrum occurs, more comprehensive locus-specific risk assessments can be established.

4. Management and treatment options

The treatment aspect of long QT syndrome is a fascinating area of investigation since the efficacy of the various modalities appears to depend on the underlying genotype and also on whether the QT interval prolongation is acquired or congenital. For example, polymorphic ventricular tachycardia is usually associated with bradycardia in the acquired form, whereas it tends to be associated with catecholamine surges in the congenital form [24]. The primary treatment of acquired long QT syndrome is the cessation of any precipitating drug, as well as the correction of any metabolic derangements (e.g., reversing hypokalemia, hypomagnesemia, and hypocalcemia). Examples of major offending drugs include the following: antiarrhythmic agents (quinidine, procainamide, disopyramide, amiodarone, and sotalol); antimicrobial agents (macrolide anti-
biotics, trimethoprim-sulfamethoxazole, ketoconazole, and pentamidine); antihistamine agents (terfenadine and astemizole); psychotropic agents (thioridazine, phenothiazines, and butyrophenones); motility agents (cisapride and domperidone); and miscellaneous chemical agents (organophosphate insecticides, papaverine, arsenic trioxide, and cesium chloride) [6,29]. The preceding list of culprit agents is not meant to be comprehensive but rather illustrates the point that a careful evaluation is often useful in determining the cause of an acquired long QT syndrome. A genetic predisposition to drug-provoked long QT syndrome has also been characterized in the literature. For example, polymorphisms in the KCNE1 and KCNE2 genes – genes that code for potassium channels – have been associated with long QT syndrome induced by quinidine and erythromycin [30,31]. Other mutations in the potassium channel tetrameric subunits that affect the currents, $I_{\text{Kr}}$ and $I_{\text{Ks}}$, have also been described; in the presence of certain drugs (e.g., mefloquine, halofantrine, and clarithromycin). These mutations appear to predispose to the occurrence of long QT syndrome torsades de pointes [6,31–34]. In the future, it may be possible to know which medications to avoid when a patient exhibits a specific mutation predisposing to drug-provoked long QT syndrome – torsades de pointes. However, in more than 85% of patients who manifest acquired long QT syndrome, no channel mutations have been elucidated thus far [6].

Based on the observation that physical exertion and emotional stress are significant triggers for cardiac events in the setting of congenital long QT syndrome (specifically the LQT1 and LQT2 genotypes), avoidance of competitive sports would appear to be a prudent lifestyle modification. Participation in recreational activities that do not cause abrupt increases in heart rate could be advised instead [6]. Other nonmedical measures include the avoidance of drugs known to cause QT interval prolongation and diligent replenishment during states of excessive electrolyte loss (e.g., during a diarrheal illness or during episodes of profuse perspiration).

The efficacy of pharmacologic treatment of congenital long QT syndrome appears to be modulated by the underlying genotypic substrate. Beta-adrenergic receptor antagonists appear to decrease the occurrence of syncope and sudden cardiac death in patients with congenital long QT syndrome [35]. These agents reduce torsades de pointes and may also shorten the QT interval by decreasing activation from the left stellate ganglion, a ganglion that innervates the bulk of the ventricular myocardium and relays sympathetic activity [36]. A retrospective study from the long QT syndrome registry involving 869 patients being treated via beta-adrenergic blockade revealed significant decrements in the rate of cardiac events in both probands and affected family members who received this form of pharmacotherapy [37]. However, this same study also revealed that 32% of patients who experienced cardiac events (syncope or aborted cardiac arrest) prior to initiation of beta-blockade experienced another cardiac event during the 5-year period while receiving beta-blockade; the hazard ratio was calculated to be 5.8 when this cohort was compared with the cohort that was asymptomatic in terms of cardiac events prior to commencement of beta-blockade therapy [36,37]. Furthermore, recurrent aborted sudden cardiac death episodes occurred in 14% of patients who had a history of aborted sudden cardiac death before therapy was initiated (hazard ratio 12.9 when compared to the asymptomatic cohort) [36,37]. Thus, a significant rate of recurrent cardiac events is still present despite beta-blockade therapy, especially in those patients who were symptomatic before therapy. Patients in this subset are good candidates for implantable cardioverter defibrillator therapy in order to prevent sudden cardiac death [38–40]. The recurrence of cardiac events exhibited in the above-cited study may partially stem from the variable efficacy of beta-blockade in the presence of different genotypic substrates [26,36,41]. In animal models that correspond to the LQT1, LQT2, and LQT3 gene mutations, beta-adrenergic stimulation induced torsades de pointes in LQT1 and LQT2 (via enhancement of transmural dispersion of repolarization) while it suppressed torsades de pointes in LQT3 (via a decrease in transmural dispersion of repolarization). Conversely, the use of a beta-adrenergic receptor antagonist like propranolol prevented the induction of torsades de pointes in LQT1 and LQT2 but facilitated its induction in LQT3 [36,42].

A surgical intervention has been utilized in an effort to interrupt the transmission of sympathetic activity to the myocardium. The procedure is termed “left cervicothoracic sympathectomy” (LCTZ) and results in significant cardiac denervation with an associated Horner’s syndrome. Studies indicate that this treatment is effective but not completely protective [15,36]. In light of recent evidence implicating ionic channel mutations as the primary etiologic cause of the congenital long QT syndrome, the role of imbalance within the cardiac autonomic nervous system and the ensuing rationale for treating this imbalance via left cardiac surgical denervation have become less important [6].

In some patients with the congenital long QT syndrome, particularly those with the LQT3 genotype, bradycardia or sinus pauses appear to be triggers for torsades de pointes [6,24,43,44]. In view of this evidence, permanent cardiac pacing has been advocated as an adjuvant therapy to beta-blockade in patients who exhibit bradycardia or atrioventricular conduction disturbances or in patients who carry the SCN5A mutation (responsible for the LQT3 genotype of congenital long QT syndrome) [6,45–52]. At this juncture, cardiac pacing should be implemented to fulfill two criteria: (1) prevention of bradycardia by utilizing a high lower rate limit ($\geq 80$ bpm); and (2) prevention of pauses via the usage of pause-prevention pacing techniques such as rate-smoothing [6,51].

Recent advances have also suggested novel therapeutic interventions that could target specific abnormal ion channels involved in the pathogenesis of this disease.
spectrum. For example, mexiletine, a class IB antiarrhythmic agent that blocks sodium channels, causes a greater shortening of the QT interval in patients with LQT3 than in those with LQT1 and LQT2 [53]. Increasing the serum potassium concentration via the dual administration of intravenous potassium and spironolactone can cause significant reductions in the QTc values in patients with the LQT2 genotype [54]. However, the maintenance of a 1.5 meq/L or higher elevation in serum potassium level does not seem to be a practical and viable option for long-term therapy. Nicorandil, an agent that induces potassium channel opening, appears to normalize repolarization abnormalities caused by epinephrine infusion in patients with the LQT1 genotype [55]. The impact of the novel class of antiarrhythmic agents (e.g., ivabradine) that inhibit the I(f) current of the sinoatrial node and thereby reduce heart rate and ischemia would also be an interesting area of investigation. Animal studies indicate that ivabradine does not affect cardiac contractility since it is a selective and specific inhibitor of the inward I(f) current, which makes an important contribution to sinoatrial nodal pacemaker activity [59,60]. However, whether this agent can actually decrease the risk of torsades de pointes in individuals harboring the LQT1 and LQT2 genotypes (as can other negative chronotropic agents like beta-adrenergic receptor blockers) is an intriguing question. No study in the current medical literature addresses this question. At this juncture, the evidence for all of the above-mentioned novel therapeutic agents is preliminary. Long-term studies will need to be conducted in order to ascertain their true efficacy in lessening morbidity and mortality.

5. Summary

The long QT syndrome is not a single disease entity; rather, it consists of a spectrum of variant entities. This heterogeneity stems from the presence of different mutations in the genes that encode cardiac ion channels. These mutations appear to produce a common final aberrant phenomenon: an abnormal prolongation of the repolarization phase in the cardiac action potential. This phenomenon can lead to clinical manifestations of lengthening of the QT interval on the surface electrocardiogram, syncopal episodes, and sudden cardiac death from torsades de pointes. The triggering events, prognosis, and risk stratification of patients with long QT syndrome appear to be influenced by the underlying genotype. The primary treatment of congenital long QT syndrome – beta-blockade therapy with internal cardioverter defibrillator therapy – appears to be useful in a subset of patients. Novel therapeutic agents that target specific abnormal ion channels are in a preliminary phase of investigation. In the future, the formulation of a distinct treatment protocol, as dictated by a patient’s specific genetic substrate, may become the optimal modality in managing this potentially lethal disease.

References
