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The Etiology & Management of Long QT Syndrome

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ABSTRACT:
Long QT Syndrome (LQTS) is a congenital or acquired condition of the heart rhythm which is characterized on an electrocardiogram by a long QT interval and a type of ventricular tachycardia known as Torsades de Pointes (TdP). The pathophysiology of LQTS may be based in either increases in sympathetic activity in the electrical conduction system, or in abnormal ion flow within the heart, which lead to increases in action potential duration and subsequently prolongs the QT interval, causing predisposition to TdP. LQTS can result from inherited genetic mutations but can also be acquired due to medications such as Class I and Class III antiarrhythmics. Treatment for the condition includes beta-blocker medications, sympathetic denervation procedures, and cardioverter-defibrillator implants. LQTS is of particular interest due to its ability to lead to TdP, which can lead to unconsciousness or sudden cardiac death, and because of its typical onset and severity without other clinical signs which often leads to misdiagnosis. Work must be continued to investigate the drugs which can cause the acquired form of this disease, the genetics of the disease, and the best treatment for varying severities of the disease in order to improve patient outcomes
Keywords: Long QT syndrome; Torsades de pointes; ion flow; congenital; acquired; parasympathetic

INTRODUCTION:

Long QT Syndrome (LQTS) is an abnormality of the electrical conduction system of the heart that can be congenital or acquired as an adverse response to medication, metabolic abnormalities, or bradyarrhythmias. This defect is characterized by a prolonged QT interval that pre-disposes affected individuals to a specific polymorphic ventricular tachycardia (VT), 'Torsades de pointes' (Tdp), which leads to sudden loss of consciousness and may result in sudden cardiac death. The presenting symptoms commonly begin in pre-teen to teen-age years and typically occur during physical activity or strong emotional states. The syncopal episodes are often misdiagnosed as an ordinary faint or a seizure. The frequency of Long QT is unknown

but it appears to be a common cause of sudden and unexplained death in children and young adults. It is much more common than previously thought, possibly as frequent as 1 in 5,000, and may cause 3,000-4,000 sudden deaths in children and young adults each year in the United States.

PATHOPHYSIOLOGY:

One of the possible mechanisms underlying the LQTS came from the observation that the immediate trigger for TdP in the inherited form is often a sudden surge in sympathetic tone [1]. This led to the hypothesis that the congenital LQTS may be caused by an imbalance in the sympathetic innervation of the heart. Another hypothesis focuses on possible genetically based derangements in cardiac ion flows, resulting in prolongation of the action potential [2].

INCREASED PARASYMPATHETIC ACTIVITY:

The activity of the left sympathetic stellate ganglion is greater than that of the right ganglion in normal individuals. An increase in activity of the left stellate ganglion or elimination of the right stellate ganglion leads to increased sympathetic innervation of the heart. A right stellectomy or stimulation of the left stellate ganglion prolongs the QT interval with a T wave morphology that mimics the surface ECG found in patients with LQTS [3]. Automated T wave morphology analysis has been recently shown to accurately distinguish between patients with and without LQTS, as well as between two subtypes of LQTS, permitting better understanding of the T wave morphologies which characterize the disorder as influenced by sympathetic innervation [4].

Sympathetic stimulation facilitates the induction of TdP by decreasing the refractory period, permitting premature stimulation, and allowing reentry in the presence of the shorter refractory period that had been further shortened by the earlier excitation. In addition, an accelerating rate results in successive responses that are premature with respect to the preceding ones, not due to the prolongation of the QT interval specifically, but rather due to dispersion of repolarization.

Clinical evidence supports the hypothesis that increased sympathetic activity may underlie the pathophysiology of LQTS [3] [5]. Antiadrenergic therapies, including beta-blockers and left sympathectomy, substantially reduce the risk of TdP in patients with LQTS by decreasing sympathetic activation from the left stellate ganglion and shortening the QT interval [6].

DERANGEMENTS IN ION FLOW:

A second hypothesis focuses on possible derangements in ion flow, leading to increases in action potential duration (APDs) which presumably prolong the QT interval and allow entry into Tdp. Increased APDs responsible for QT interval prolongation and subsequent Tdp are most often caused by increased depolarizing sodium influx or decreased repolarizing potassium efflux due to modified ion channel activity. Such gain or loss of sodium or potassium ion channel activity, respectively, can predispose the cell to early afterdepolarizations (EADs), and occasionally, to delayed afterdepolarizations (DADs) [7]. After polarizations are single or multiple oscillations of the membrane potential that can occur during phases 2 or 3 of the action potential due to preceding transmembrane activity [8]. Such EADs and DADs can lead to spontaneous action potentials, or triggered responses, which underlie arrhythmias such as Tdp, potentially leading to sudden cardiac death.

Prolongation of repolarization results from a net reduction in the outward current, which is due to an increase in inward current, a decrease in outward current, or both. This may occur by one of three ionic mechanisms. One mechanism is the activation of a delayed sodium current that occurs early during repolarization. This is the mechanism responsible for the QT prolongation seen with the drug ibutilide, a class III antiarrhythmic drug [9, 10]. An increased inward calcium current is caused by an elevation in transsarcolemmal calcium current due to either catecholamines or a rise in the extracellular

calcium concentration. A decreased outward potassium current can be caused by either Class IA or III antiarrhythmic drugs [11]. Class IA antiarrhythmic agents (quinidine, procainamide, and disopyramide) block the outward delayed rectifier potassium current; in contrast, Class III antiarrhythmic drugs (such as sotalol) block the rapid component of the delayed outward rectifier with a minimal effect on the inward current.

Triggered responses or triggered activities are EADs that reach threshold potential, depolarize cell membranes, and result in action potentials. Propagation of these EADs produce premature ventricular depolarizations that may initiate TdP in susceptible subjects. EADs are particularly easy to induce in Purkinje fibers and myocardium due to events prolonging APDs [8]. It is believed that EADs and triggered activity are the initiating mechanism for the ventricular ectopy and polymorphic VT associated with long QT intervals [12]. The mechanism that sustains general arrhythmias may also be triggered activity, reentry, or abnormal automaticity. TdP tends to arise due to triggered activity, and can be initiated through various modes, which are characterized by their cycle lengths, timing of initiating premature ventricular contractions, and RR intervals; each mode of initiation proceeds via a different mechanism [13].

Maintenance of TdP is thought to result from a combination of variable spatial expression of ion channels and variable patterns of gap junctions which sustain the arrhythmia [14]. TdP may be sustained by either focal activity alone, or by reentry mechanisms/circuits as well. Research suggests that reentry may be a predominant mechanism by which TdP is sustained, as electrically induced ventricular tachycardias (VTs) resemble clinical features of LQTS, in that: (a) both are more easily induced when APDs are prolonged, and (b) reduced repolarization dispersion leads to a greater chance of spontaneous termination in both cases [15]. However, focal activity may be sufficient to sustain TdP, depending on the degree of action potential heterogeneity. If the degree of heterogeneity is small, the reentry circuit may be responsible for Tdp maintenance, whereas if the degree of heterogeneity is large, focal activity alone may be sufficient [16].

ETIOLOGY:

CONGENITAL PROLONGED QT SYNDROME:

Modern molecular biological techniques have permitted the recent identification and analysis of fifteen of the genes responsible for some of the congenital long QT syndromes. Analysis of different families have linked the expression of the LQTS phenotype to at least 15 loci, on chromosomes 11, 7, 3, 4, 21, 17, 12, and 20, confirming the presence of genetically heterogeneous subtypes of the disorder [17, 18]. The genes/gene products affected in each of the fifteen syndromes are as follows: KCNQ1, HERG, SCN5A, Ankyrin B, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP9, SNTA1, KCNJ5, calmodulin, and triading. The three most common of these LQTS subtypes are LQTS 1 (30-35% of cases), LQTS 2 (25-30% of cases), and LQTS 3 (5-10% of cases), which are discussed in the following section [19, 20]. Ninety percent of mutations causing LQTS are found in LQTS 1, LQTS 2, and LQTS 3 [21]. Patients with clinical phenotypes consistent with the Jervell-Lange-Nielsen (LQTS associated with congenital deafness, inherited as an autosomal recessive trait) or Romano-Ward syndromes (LQTS without deafness inherited as an autosomal dominant trait) may have any of the underlying mutations found in LQTS. There is also a homozygous KCNQ1 mutation in which QT prolongation and deafness are inherited as autosomal recessive traits.

The LQTS1 phenotype is located on the short arm of chromosome 11 and the involved gene is KCNQ1 [20]. The protein product of this gene codes for the alpha-subunit of the slowly acting outward-rectifying potassium channel, and when co-expressed with the cardiac protein minK, forms the slowly acting component of the outward-rectifying potassium current [18, 22].

Suppression of the outward-rectifying potassium current by mutations in the KCNQ1 gene, in the absence or presence of minK, can be correlated with prolongation of human ventricular action potentials [23]. Mutations in the gene for minK, called LQTS 5, produce a similar defect in the potassium current. There is wide KCNQ1 allelic heterogeneity and 16 missense mutations. Homozygous mutations of KCNQ1 appear to cause the Jervell-Lange-Nielsen syndrome.

LQTS 2 is caused by mutations in a potassium channel gene localized to chromosome 7. The region on chromosome 7 is the human eag-related gene or HERG, the function of which is the rapidly acting component of the outward-rectifying potassium current [20]. This current is largely responsible for repolarization and thus for the QT interval duration; LQTS mutants can be rescued by pharmacological agents which restore HERG channels to the membrane and therefore restore repolarization activity, preventing arrhythmias [24, 25].

LQTS 3 is caused by mutations in the sodium channel gene (SCN5A) located on chromosome 3 [20]. Mutations involve a region of the sodium channel gene that causes impaired inactivation of the channel. The abnormal sodium channel fails to inactivate only 3.5 percent of the time, suggesting that infrequent dysfunction can result in a clinical phenotype [26]. Impaired sodium channel inactivation keeps the membrane slightly depolarized through slow leakage of sodium current into the cell, possibly resulting in membrane instability and EADs. Brugada syndrome is also caused by a defect in the SCN5A gene which may either cause arrhythmias through a repolarization or depolarization hypothesis, both of which have ex vivo and in vivo experimental evidence supporting their mechanisms. In the repolarization hypothesis, the genetic defect may lead to dispersion in repolarization across the ventricular wall, leading to a shorter action potential and allow currents during the plateau phase [27]. The depolarization hypothesis suggests instead that factors such as reduced sodium supply may contribute to conduction delays in the right ventricular outflow tract. A sporadic SCN5A mutation, R1623Q, has also been described. In contrast to the heritable mutations, this mutation results in a prolonged opening and early reopening of the sodium channel and therefore a threefold prolongation of sodium current decay [28].

Although there are 15 identified genes responsible for the LQTS, multiple mutations in each of these genes have been identified: 88 in KCNQ1, 89 in HERG, and 32 in SCN5A; as a result, screening high-risk groups is difficult [29]. It has been proposed that drug-induced LQTS might represent a genetically mediated "acquired" form of LQTS; support for this comes from an observation that there are a relatively large number of individuals carrying silent mutations on LQTS genes [30]. In such individuals, the LQTS mutations may produce an alteration in repolarizing currents that is insufficient to prolong the QT interval at rest but which becomes prolonged by any drug that affects potassium currents; the occurrence of such QT prolongation can precipitate the onset of TdP [31].

ACQUIRED PROLONGED QT SYNDROME:

Development of EADs and QT interval prolongation are potentiated by bradycardia, hypokalemia, hypomagnesemia, and medications [32]. Bradycardia is associated with increased inactivation of the outward repolarizing potassium current and a reduction in the Na-K-ATPase pump outward current. Slow heart rates also enhance the activity of certain antiarrhythmic drugs on repolarization by prolonging repolarization and the QT interval. This property is called reverse use dependence and can lead to ion fluxes that facilitate EADs and TdP [33]. Hypokalemia leads to decreased outward repolarizing current, and a subsequently longer QT interval, via reductions in electrogenic Na-K-ATPase pump activity and outward potassium channel activity [34].

Class IA antiarrhythmic agents block both inward sodium and outward potassium channels, while

Class III antiarrhythmic drugs block potassium channels. Blockade of sodium channels would be expected to shorten the action potential duration, whereas blockade of potassium channels should prolong the action potential duration. At slow heart rates and low to normal concentrations of Class IA drugs, the potassium channel blocking activity predominates over the effect on the sodium channel [35]. Therefore, EADs and TdP are more frequently seen with nontoxic levels of quinidine; supratherapeutic levels lead to increased sodium channel blocking activity and are rarely associated with QT prolongation and TdP [36].

Class III agents are potassium channel blockers that cause QT prolongation and are associated with TdP [33]. Class III antiarrhythmic agents prolong the time for repolarization in atrial and ventricular myocardium. This effect is mediated by activation of a slow delayed inward sodium current that occurs early during repolarization. Other class III agents act by inhibiting outward potassium currents.

The degree of drug-induced blockade of the rapidly activating delayed rectifier current appears to be dependent upon the extracellular potassium concentration [37]. Low extracellular potassium increases the drug block, while there is relative resistance to block when extracellular potassium levels are elevated as may occur with myocardial ischemia or rapid heart rates. This relationship may explain the reverse use-dependent effect of these drugs, which is that the degree of prolongation of repolarization is reduced as the stimulation rate increases.

Ketoconazole and erythromycin both inhibit the P450 3A isoform of the hepatic P450 system. Individuals with low isoform activity may therefore be unable to oxidize drugs such as terfenadine, astemizole, or disopyramide when they are concurrently taking ketoconazole or erythromycin. These effects may lead to QT prolongation, resulting in TdP [37]. In addition, erythromycin alone can cause QT prolongation and TdP [38].

QT prolongation and TdP have been reported in patients with HIV infection, even in the absence of drug therapy [39, 40]. Postulated mechanisms include myocarditis, a subclinical cardiomyopathy, or autonomic neuropathy [41].

As mentioned previously, both the dispersion of repolarization and reentry may be other potential mechanisms for the propagation of TdP. Cells in the myocardium demonstrate marked prolongation of action potential duration in response to drugs such as quinidine, sotalol, and erythromycin. Dispersion of repolarization could therefore occur in response to these drugs if the action potential is prolonged in these cells but not in the surrounding area. The result is a functional block in the myocardium, providing the necessary milieu for the development of a reentrant arrhythmia [42].

PATHOPHYSIOLOGIC DIFFERENCES BETWEEN THE ACQUIRED AND CONGENITAL FORMS OF LQTS.

The polymorphic VT in the acquired form of LQTS is most commonly precipitated by long-short RR intervals [43]. This interval is normally caused by a ventricular premature beat followed by a compensatory pause. Polymorphic VT can also occur in association with bradycardia or frequent pauses; as a result, the acquired form of LQTS is called "pause-dependent" LQTS [44]. The inherited or congenital form of LQTS typically results in arrhythmias following a sudden adrenergic surge [45]. However, these distinctions are not absolute, since there may be overlap between the two disorders within an individual patient.

DIAGNOSIS:

Although the method of diagnosis is the electrocardiogram, most young, healthy people do not routinely undergo this test, and, thus, their first, and possibly fatal, episode of LQTS comes without warning. In a number of cases, a non-fatal episode can be mistakenly treated as a seizure, and, therefore, a follow-up assessment does not include an electrocardiogram [46-48]. Triggers of cardiac events associated with LQTS

include increased heart rate due to exercise or excitement, whereas other events occur during rest or sleep. LQTS 1 primarily occurs as triggered by exercise, LQTS 2 primarily occurs resulting from high heart rate due to excitement, and LQTS 3 primarily occurs during sleep or rest [17].

In patients who have suffered cardiac events potentially related to LQTS, steps in diagnosis include an exercise electrocardiogram which would show abnormal ventricular repolarization (visualized as QT prolongation or T-wave abnormality) and Tds [49]. Family history of LQTS and clinical history of syncope or congenital deafness are additional considered factors [17]. In all instances where an individual is diagnosed with LQTS, family members should be thoroughly evaluated, and a detailed family history should be taken noting any individuals with episodes of sudden loss of consciousness and any cases of unexplained sudden death. In addition to LQTS, other causes of sudden death with similar presentations include other ion channelopathies, such as Brugada syndrome, short QT syndrome, and catecholaminergic polymorphic ventricular tachycardia, as well as cardiomyopathies, such as hypertrophic cardiomyopathy [50]. Patients with these syndromes may present with arrhythmias, seizures, fatigue, and cardiac arrest; features visible on routine electrocardiograms can differentiate these diseases from one another and from other etiologies.

TREATMENT AND MANAGEMENT:

Beta-blockers are drugs of choice for patients with LQTS [51, 52]. The protective effect of beta-blockers is related to their adrenergic blockade diminishing the risk of cardiac arrhythmias. Beta-blockers are effective in preventing cardiac events in approximately 70% of patients, while cardiac events continue to occur despite beta-blocker therapy in the remaining 30% of patients [52]. Although propranolol and nadolol are the most frequently used beta-blockers for the condition, the effectiveness of propranolol is presently disputed, and nadolol is not currently available worldwide [53]. Other beta-blockers commonly used to treat LQTS include metoprolol and atenolol, which have recently been suggested as superior to the previously recommended propranolol.

Implantation of cardioverter-defibrillators appears to be an effective therapy for high-risk patients, defined as those with aborted cardiac arrest or recurrent cardiac events despite conventional therapy (i.e., beta-blocker alone), or beta-blockers in combination with pacemaker and/or stellectomy. Implantation of cardiac pacemakers (with ventricular or dual chamber pacing) has been considered a helpful therapeutic strategy based on the premise that pacing eliminates arrhythmogenic bradycardia, decreases heart rate irregularities (eliminating short-long-short series), and decreases repolarization heterogeneity, therefore diminishing the risk of Tdp ventricular tachycardia [54]. The American College of Cardiology/American Heart Association/ European Society of Cardiology practice guidelines recommend ICD implantation for high-risk patients, and appropriate ICD shocks are found in patients with LQTS, demonstrating a positive therapeutic effect [11, 55]. However, due to repeated additional cardiac events even after ICD implantation as well as additional inappropriate shocks in some cases, specific definitions of “high-risk” patients and criteria for implantation must be clarified. Further, most LQTS patients can be treated effectively without ICD implantation; beta-blockers should first be attempted particularly in younger patients [56].

Sympathetic denervation procedures, including left cervicothoracic stellectomy and left thoracoscopic sympathectomy, are additional antiadrenergic therapeutic measures used in high-risk patients with LQTS [57-60]. Sympathetic denervation is highly effective, though not entirely curative, as patients who undergo sympathetic denervation often suffer cardiac events post-procedurally [61, 62]. Sympathetic denervation decreases the risk of cardiac events in high-risk patients with LQTS, potentially due to an antitorsadogenic effect resulting from

restoration of electromechanical order [57]. In some high-risk patients, combination therapy can be used consisting of beta-blockers, stellectomy, and/or implantation of cardioverter-defibrillator with cardiac pacing function [52, 63, 64].

CONCLUSION:

Because of the sudden and often unpredicted onset of TdP in LQTS patients, as well as the severity of the condition's symptoms, it is particularly important to continue study of this disease state, including how to treat and manage it. Similarly, work must continue to evaluate the drugs which can affect and induce LQTS symptoms and populations which may be more at risk for developing acquired LQTS to help prevent the acquired version of the disease. It is especially necessary to continue study of this condition's genetic basis to best diagnose patients, as this will facilitate earlier diagnosis and better patient genetic screenings. Combined, these efforts will help prevent misdiagnosis upon initial symptom presentation, or, more optimally, to allow management of the disease prior to symptom onset.

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