Congenital Long and Short QT Syndromes

Andrew J. Brenyo   David T. Huang   Mehmet K. Aktas

Department of Cardiovascular Diseases, University of Rochester Medical Center, Strong Memorial Hospital, Rochester, N.Y., USA

Abstract

Congenital long and short QT syndromes are familial arrhythmias characterized by derangement of repolarization and a high risk of sudden cardiac death due to ventricular tachyarrhythmias. With growing understanding of these syndromes in both the medical and lay communities, diagnostic and therapeutic difficulties are increasingly faced by health care providers. Modern genomics has determined the mechanism of arrhythmia induction in these patients, resulting in specific medical therapies and improved risk stratification. This paper reviews the common presentations, genetic etiology, basic evaluation, risk stratification, and therapeutic approach for both syndromes. Particular attention is paid to the effect of the individual syndrome on the cardiac action potential and its correlate the surface 12 lead ECG. In conclusion, patients with long and short QT syndromes are at risk for sudden death, with accurate diagnosis, risk stratification, and resulting appropriate therapy favorably altering their outcome.   Copyright © 2012 S. Karger AG, Basel

Introduction

Congenital long QT syndrome (LQTS) is a genetic condition characterized by a prolonged QT interval on the surface ECG and is associated with a high risk of sudden cardiac death (SCD) due to ventricular tachyarrhythmias. Mutations within 13 identified genes cause a variety of channelopathies affecting myocardial repolarization, resulting in QT prolongation [1]. Conversely, gain-of-function mutations in a specific few of these genes result in shortening of the QT interval and myocardial repolarization. Short QT syndrome (SQTS) is characterized by constantly short QTc intervals (<300 ms) and a high familial incidence of palpitations, syncope, SCD, and atrial fibrillation [2]. In this review article we present common clinical scenarios of patients with LQTS and SQTS, review their pathophysiology, and discuss the diagnostic workup and subsequent treatment options. Future and emerging therapeutic options for patients with congenital LQTS and SQTS are also mentioned.

Common Clinical Presentations

Patients with LQTS and SQTS will present along a spectrum of illness ranging from an incidental ECG finding in an asymptomatic patient to an abnormal QT inter-

Andrew J. Brenyo, MD
University of Rochester Medical Center, Strong Memorial Hospital
Department of Cardiovascular Diseases, 601 Elmwood Avenue, Box 679-C
Rochester, NY 14642 (USA)
Tel. +1 585 275 4776, E-Mail Andrew_Brenyo@urmc.rochester.edu

val post-cardiac arrest. Any history of arrhythmic syncope (drop attacks), family history of SCD, or inherited arrhythmias should be sought. Beyond the most commonly encountered incidentally identified QT abnormalities, discovery of abnormal QT intervals upon ECG screening after the onset of syncope or the diagnosis of a family member are likely the most frequent reasons for presentation to a cardiovascular specialist.

Historically, atypical initial presentations of patients eventually diagnosed with LQTS, such as a long-standing history of syncope and recurrent 'seizures' despite antiepileptic therapy, have not been uncommon. Classic situational arrhythmic/syncopal triggers have been well described to be associated with specific LQTS types and should be investigated upon initial presentation. Arrhythmic events associated with LQT1 are triggered by swimming or other exercise, whereas most events in LQT2 and LQT3 are associated with acute arousal or sleep/rest without arousal [3–5].

SQTS presentation differs from LQTS in that the symptomatic patient will often note onset of atrial fibrillation and palpitations at a young age potentially independent of a history of syncope [6]. Also in contrast to LQTS, no specific situational arrhythmic triggers have been identified for the SQTS phenotype and the terminal ventricular arrhythmia is typically ventricular fibrillation in SQTS and torsades de pointes in LQTS.

Epidemiology

Historically, congenital LQTS was thought to be a rare disorder in part because only patients with the most severe QT prolongation were detected and reported. However, it is estimated that at least 1/2,500 to 1/7,000 people worldwide are affected with LQTS [7]. As awareness and screening for LQTS improves, its prevalence is expected to increase. Insufficient data is available to suggest worldwide, racial, or ethnic variation in prevalence. LQTS is more commonly diagnosed in women, potentially inaccurately secondary to the sex-based differences in the upper limit for the QTc interval in post-pubertal females compared to males (460 and 440 ms, respectively) [8].

Congenital short QT syndrome was first reported as a cause for increased risk of sudden death in 2000 [2], and at this time determinations of its incidence and prevalence are difficult to make due to limited data. With the increased use of patient registries such as the European SQTS Registry [9], characterization of the prevalence and incidence of SQTS should be possible.

Etiology

Long QT Syndrome

Congenital LQTS is inherited as a monogenic disorder with primarily autosomal dominant inheritance and variable penetrance [10]. About 85% of the reported cases are inherited from one of the parents, with the remaining 15% of affected patients having de novo mutations. Mutations identified in 13 different genes account for congenital LQTS, with LQT1, LQT2, and LQT3 mutations constituting 90–95% of cases (table 1) [1]. These mutations cause alterations in specific ion channels active during the normal action potential (fig. 1a) leading to the pathophysiologic alteration of repolarization, manifested as a prolongation of the QT interval on the ECG.

LQT1 results from a loss-of-function mutation in the *KCNQ1* gene which encodes the alpha-subunit of the slow activating potassium channel responsible for the IKs current. *KCNQ1* mutations are the most commonly identified in genotyped patients. A homozygous mutation in *KCNQ1* results in the rare autosomal recessive Jervell and Lange-Nielsen syndrome (JLNS) [11, 12] that is associated with congenital deafness and a high rate of fatal cardiac events [13]. Dysfunctional IKs channels lead to dispersion of repolarization (fig. 1b) from the epicardial to the endocardial surface, potentiating the development of ventricular tachyarrhythmias. Electrocardiographically, there is a characteristic prolonged QT interval associated with a broad based T wave (fig. 2).

The LQT2 phenotype arises from mutations in the *KCNH2* gene encoding the alpha (HERG) subunit of the potassium channel responsible for the IKr current. *KCNH2* mutations are the second most commonly identified, accounting for up to 35–40% of genotyped patients [7, 14]. Dysfunctional IKr channels (fig. 1b) lead to slowing and transmural dispersion of repolarization which predisposes patients to ventricular tachyarrhythmias, particularly torsades de pointes. Electrocardiographically, a prolonged QT interval is seen with characteristic low amplitude and notched T waves often visualized best in the limb leads or rhythm strip (fig. 3).

LQT3 stems from gain-of-function mutations in the *SCN5A* gene which encode for rapidly inactivating sodium channels, allowing an inward flow of sodium ions to persist long into the plateau phase of the action potential and thereby prolonging repolarization (fig. 1b). Electrocardiographically, there are characteristic long ST segments with a late appearing T wave resulting in a long QT interval (fig. 4).
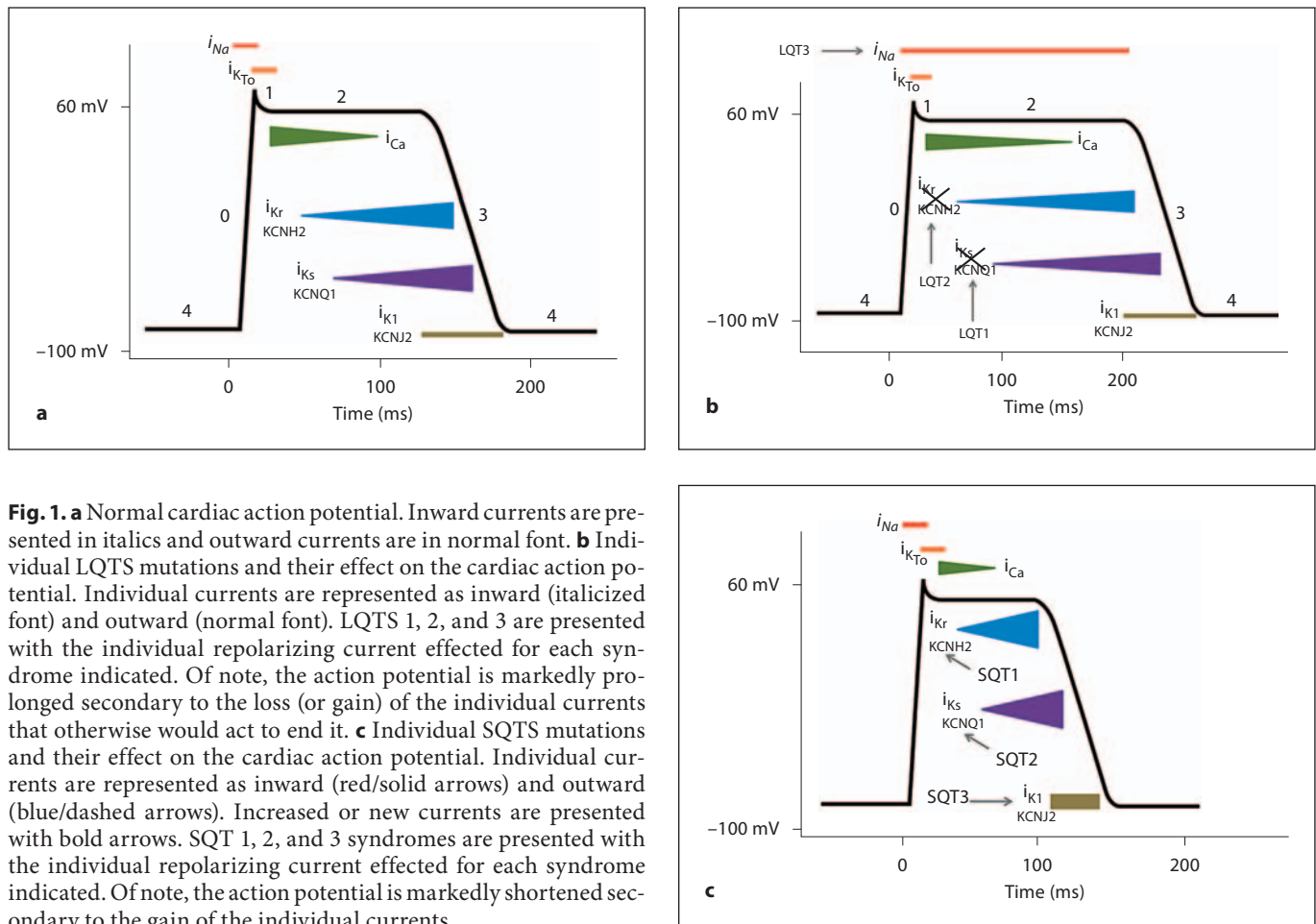
Fig. 1. a Normal cardiac action potential. Inward currents are presented in italics and outward currents are in normal font. **b** Individual LQTS mutations and their effect on the cardiac action potential. Individual currents are represented as inward (italicized font) and outward (normal font). LQTS 1, 2, and 3 are presented with the individual repolarizing current effected for each syndrome indicated. Of note, the action potential is markedly prolonged secondary to the loss (or gain) of the individual currents that otherwise would act to end it. **c** Individual SQTS mutations and their effect on the cardiac action potential. Individual currents are represented as inward (red/solid arrows) and outward (blue/dashed arrows). Increased or new currents are presented with bold arrows. SQT 1, 2, and 3 syndromes are presented with the individual repolarizing current effected for each syndrome indicated. Of note, the action potential is markedly shortened secondary to the gain of the individual currents.

Table 1. Currently identified LQTS gene mutations

| LQTS subtype	Gene mutation	Protein	Note
LQTS 1	KCNQ1	Alpha-subunit of the slow delayed rectifier potassium channel (Iks)	Most common cause of LQTS Cardiac events during exercise
LQTS 2	HERG	Alpha-subunit of the rapid delayed rectifier potassium channel (Ikr)	Second most common cause of LQTS Cardiac events occur during arousal
LQTS 3	SCN5A	Alpha-subunit of sodium channel	Cardiac events during rest/bradycardia Rarely overlaps with Brugada syndrome
LQTS 4	AnkyrinB	Adaptor proteins connecting membrane proteins to the spectrin-actin skeleton	
LQTS 5	KCNE1	MiRP1 beta-subunit of voltage-gated potassium channel	Heterozygote mutation results in Romano-Ward syndrome Homozygote mutation results in JLNS
LQTS 6	KCNE2	MinK beta-subunit of the voltage-gated potassium channel	
LQTS 7	KCNJ2	Inward-rectifier potassium channel	Andersen-Tawil syndrome
LQTS 8	CACNA1c	Alpha-1c-subunit of the L-type calcium channel	
LQTS 9	Cav3	Caveolin 3	
LQTS 10	SCN4B	Sodium channel	
LQTS 11	AKAP9	A-kinase anchor protein 9	
LQTS 12	SNTA1	Alpha-1-syntrophin	
LQTS 13	GIRK4	G protein activated inward rectifier potassium channel 4	
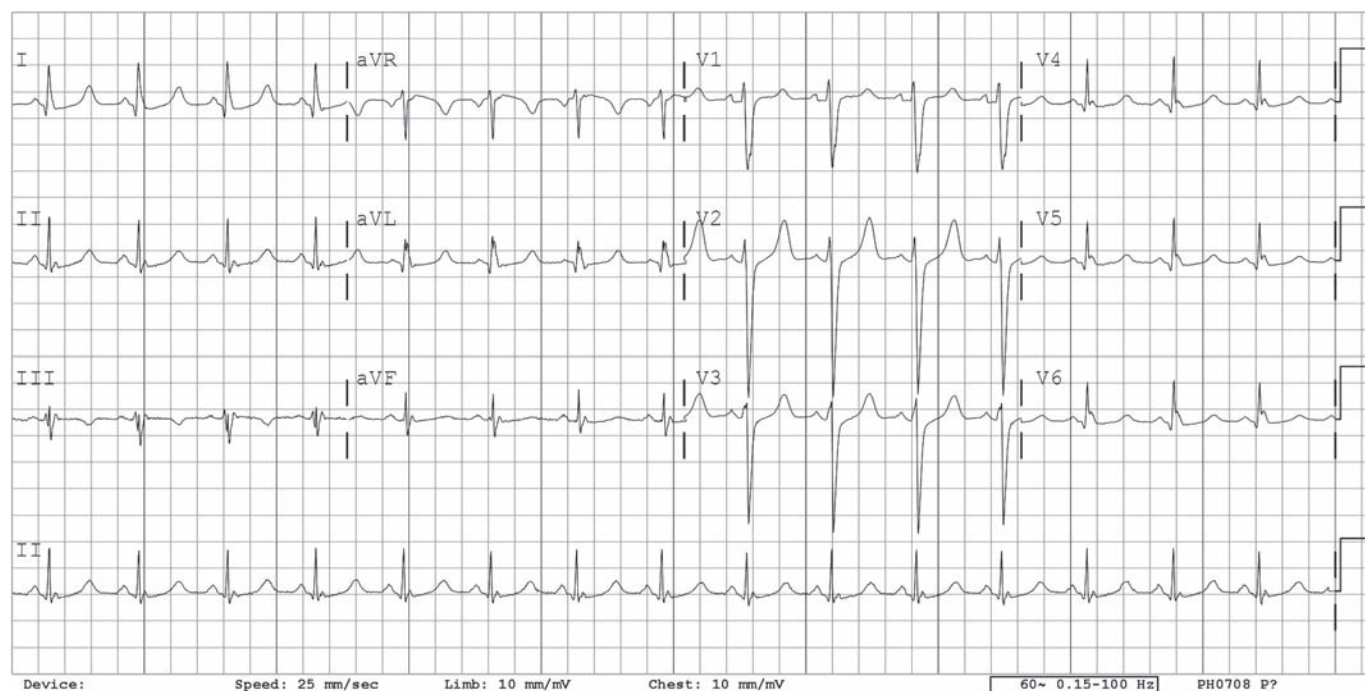
Fig. 2. Representative ECG of a patient with congenital LQTS type 1. Note broad based, peak T waves producing QT prolongation.
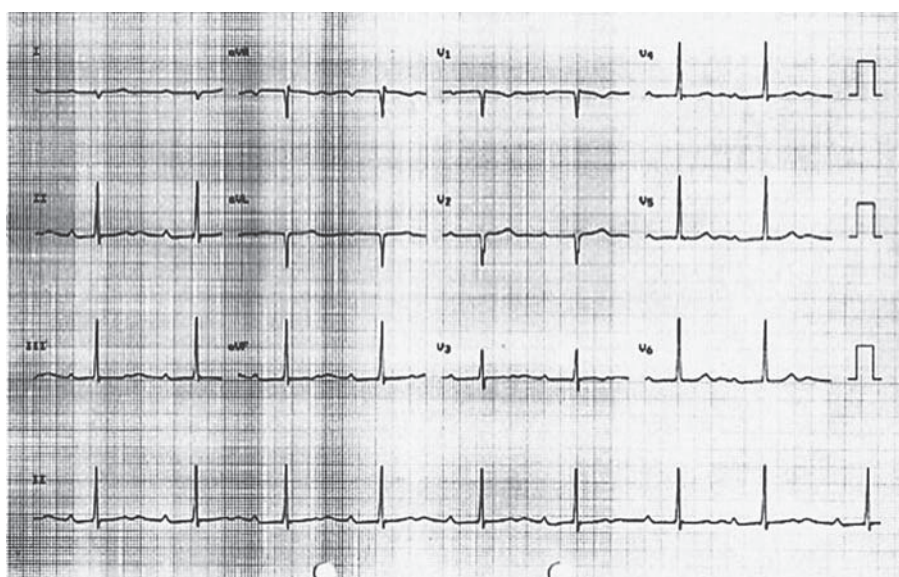
Fig. 3. Representative ECG of a patient with congenital LQTS type 2. Note the notched T waves particularly in lead II and the rhythm strip at the bottom of the ECG.

LQT4–LQT13 have been described but are responsible for less than 10% of all genotyped cases and are typically encountered only in individual families (table 1) [7].

LQTS can be phenotypically classified into 3 congenital syndromes. Romano-Ward syndrome is inherited as an autosomal dominant trait and is the most common form of LQTS. It may result from a mutation in any one of 13 identified genes and is not associated with deafness; rather, it represents the common LQTS phenotypes. JLNS is inherited as an autosomal recessive trait and results from a
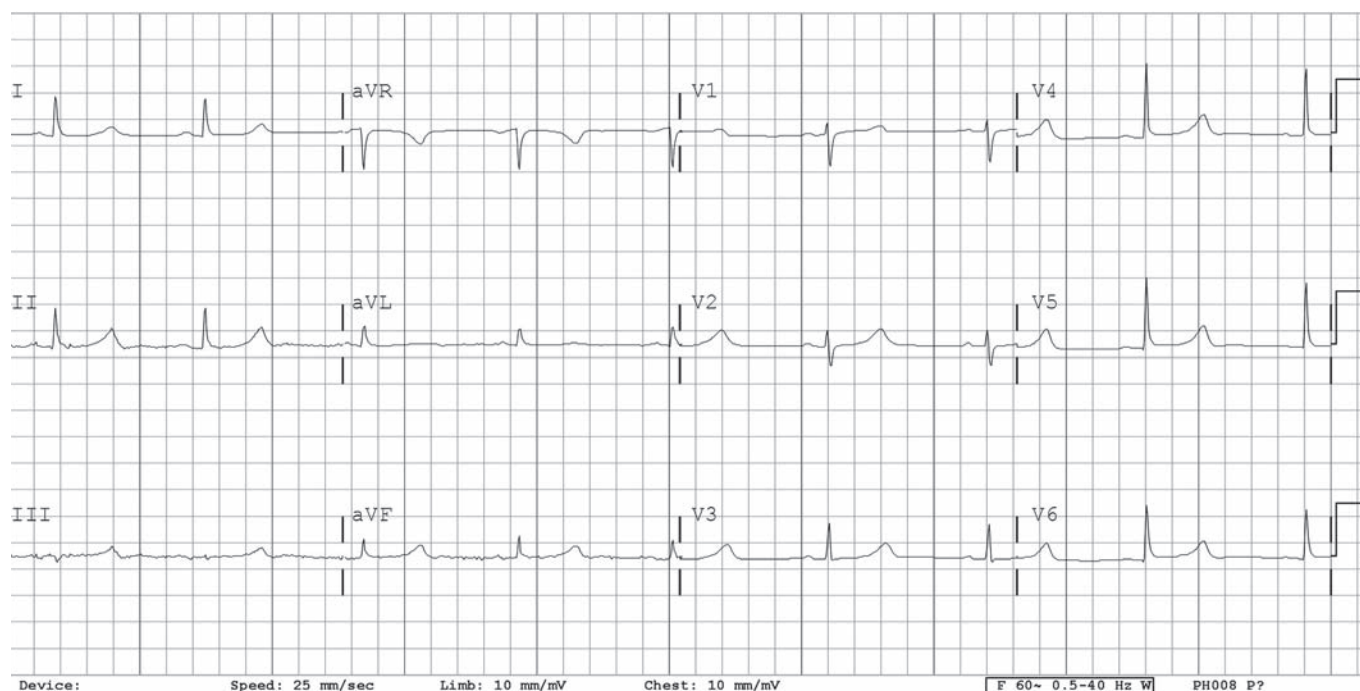
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Fig. 4. Representative ECG of a patient with congenital LQTS type 3. Note the late appearance of the T wave, after an isoelectric, long ST segment.

homozygous mutation in *KCNQ1* [11]. It is clinically characterized by a very severe form of LQTS and is associated with sensorineural deafness. Andersen-Tawil syndrome, also known as hypokalemic periodic paralysis or LQT7, is a rare autosomal dominant condition resulting from a mutation in KCNJ2 [15, 16]. These patients suffer from periodic paralysis and ventricular tachyarrhythmias and have a variety of dysmorphic features, including micrognathia, low set ears, widely spaced eyes, and clinodactyly.

Short QT Syndrome

Congenital SQTS results from autosomal dominant gain-of-function mutations in potassium channels during phases 2 and 3 of the action potential (fig. 1c) resulting in rapid cardiac repolarization. Currently we know significantly less about the genetics of SQTS compared to LQTS secondary to the rarity of SQTS. The syndrome is characterized in the few patients identified so far by a shortened QT interval of less than 300–325 ms after correction for heart rate at rates below 80 beats/min (fig. 5). A number of gain-of-function mutations have been identified within the three culprit voltage-gated potassium channel genes: *KCNH2, KCNQ1,* and *KCNJ2.* The gain of function results in a greater than normal efflux of potassium from the cell during the repolarization phase and a

shortening of the action potential. SQTS has been separated into three types based upon the culprit mutation (when known): (1) the most common, *KCNH2,* labeled short QT1; (2) *KCNQ1,* short QT2, and (3) *KCNJ2,* short QT3. *KCNH2* encodes IKr, which is responsible for the rapid component of the delayed rectifier potassium current. The remaining two genes implicated in short QT syndrome *(KCNQ1* and *KCNJ2)* have, to date, been identified only in single index cases [17, 18]. Probands reported in the literature are genotype positive for one of the three described mutations *(KCNQ1, KCNJ2,* and *KCNH2)* 21% of the time, indicating that a significant proportion of causative genetic mutations remain to be identified [19].

Diagnostic Approach

The diagnostic process is similar for both LQTS and SQTS, resting primarily on historic, electrocardiographic, and genetic data with a limited role for exercise and invasive electrophysiologic testing.

Long QT Syndrome

A careful focused history is necessary for the diagnosis of LQTS and potentially may even identify its subtype.
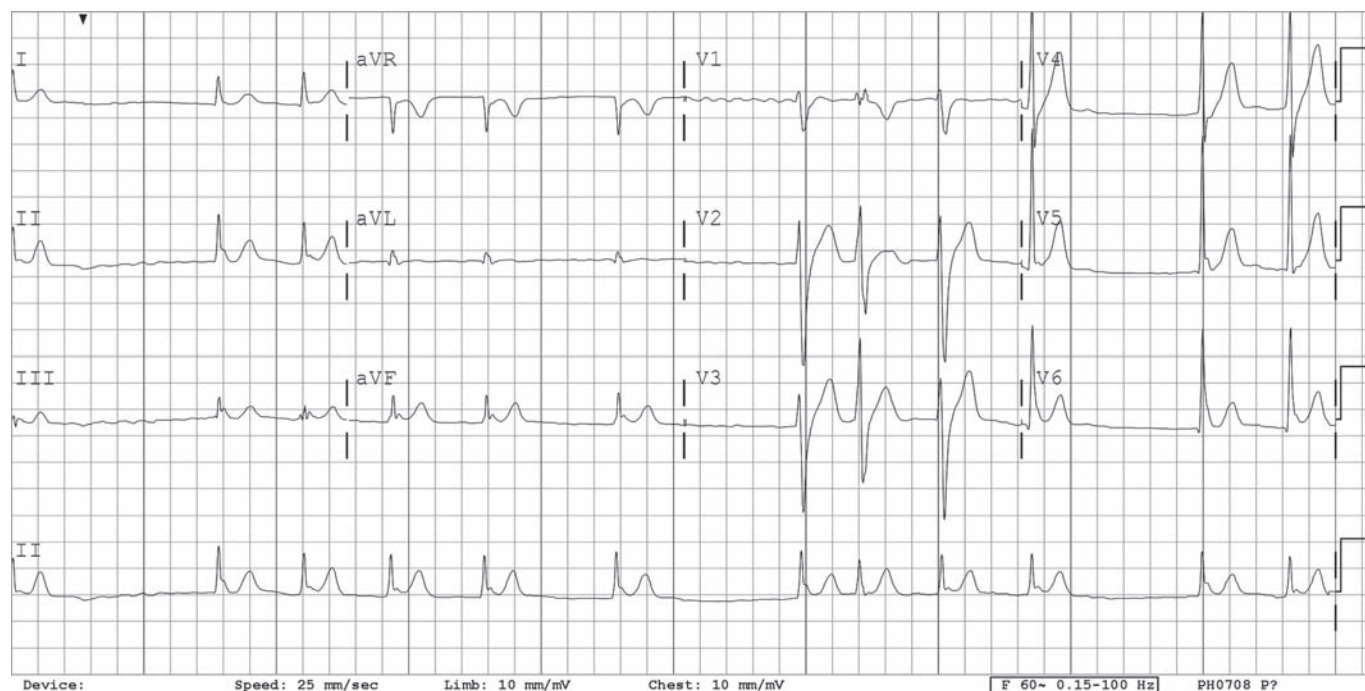
Fig. 5. Representative ECG of a patient with congenital SQTS. Note the presence of atrial fibrillation and the absence of an ST segment.

Particular attention should be paid to any episode triggers such as swimming, exercise, or arousal from sleep, all of which have classically been associated with individual LQT syndromes as discussed previously. A thorough family history with focus on any episodes of drowning, SCD, or inherited arrhythmia may be important to understand the penetrance and severity of the condition. Furthermore, the history may help elucidate potential benign causes for syncope, some of which may be completely reversible.

The electrocardiographic diagnosis of LQTS is not typically straightforward as nearly 2.5% of the normal population may have a mildly prolonged QT interval, and approximately 25% of genotype-positive LQTS patients have a normal QT interval [20]. However, the resting ECG remains crucial in the diagnosis of LQTS and should be undertaken in all suspected cases. Additionally, in a patient with documented LQTS, it is very important to obtain ECGs from parents, siblings, and any family members with pre-syncope or syncope. Developing a family pedigree utilizing this information may aid in the discovery of affected but currently asymptomatic undiagnosed family members.

Exercise treadmill testing may help to identify abnormal QT interval prolongation during exercise and into recovery. Such derangements are helpful in diagnosing LQTS, particularly LQT1 in which the QT interval and QTc increase with exercise (typically an event trigger in this population) more than those of controls or other LQT types [21]. Sy et al. [22] recently utilized an exercise-based algorithm for the diagnosis of LQT in asymptomatic relatives of LQTS probands. The combination of resting and 4-min recovery QTc in their screening algorithm yielded a sensitivity of 0.94 and a specificity of 0.90 for detecting LQTS carriers, with similar results noted in the validation cohort [22]. Furthermore, for suspected LQTS carriers (based upon a resting QTc of >470 ms) the 1-min recovery QTc allowed the authors to determine if the carrier was LQT1 ($\geq$460 ms) or LQT2 (<460 ms) genotype positive [22]. Exercise testing may also assist in the prescription of a maximum exercise level for patients presenting with exercise-induced symptoms of presyncope or syncope by simulating similar circumstances in a controlled environment.

Particularly in the setting of a concerning phenotype but normal resting and exercise QTc intervals, administration of the natural sympathetic agonist epinephrine has been utilized to unmask diagnostic changes in ventricular repolarization for LQT1 and LQT2 patients [23–26]. Three epinephrine administration techniques, i.e.

the Mayo [24], Shimizu [25], and Hekkala [26] protocols, have been reported in the literature, with similar efficacy [26]. The change in QTc, QT apex, and T wave peak durations from baseline and during epinephrine administration are calculated. The pattern of change within these parameters during provocation including shortening of the QT apex and lengthening of T wave peak and QTc intervals identifies genotype-positive patients. The Shimizu protocol has also utilized change in QTc with peak epinephrine infusion to correctly identify LQT2 genotype-positive patients [23, 25]. As of yet, epinephrine testing has not proven useful in identifying LQT3 patients and when the index of suspicion for the LQT3 genotype is high, sympathetic provocation should be forgone in favor of genetic testing [23].

Genetic testing may allow the determination of a patient's LQTS subtype through the identification of causative mutations (table 1). Knowledge of the specific gene mutation can be used in risk stratification of patients with congenital LQTS and in the prescription of medical therapy [14, 27]. Recent Heart Rhythm Society, European Heart Rhythm Association, and Canadian Heart Rhythm Society consensus statements support the use of genetic testing for symptomatic patients (post-SCD or syncope) with abnormal QTc intervals, asymptomatic patients with consistent idiopathic prolongation of the QTc interval or during provocative testing and asymptomatic first-degree relatives of genotype-positive LQT probands [28, 29]. In its current state, genetic testing is an imperfect tool due to its focus on the most common known mutations resulting in low sensitivity and its high cost. However, it remains a cornerstone of the diagnostic evaluation and risk stratification of potential LQTS patients. In contrast, investigating for inducible ventricular arrhythmias using electrophysiology studies has not been shown to have significant value in the diagnosis of patients with suspected LQTS [30].

Short QT Syndrome

Similar to LQTS, the evaluation of SQTS begins with a comprehensive history of events (syncope, presence of atrial fibrillation, and SCD) both in the patient and within the family. ECG evidence of the phenotype (short QT interval plus or minus atrial fibrillation) is also necessary for diagnosis. In contrast to LQTS, the role of genetic testing is limited in SQTS as most patients who are phenotype positive currently have unknown genetic mutations. Patients who present with electrocardiographic evidence of the short QT phenotype along with symptoms (AF or SCD) should be tested for the three most common mutations (*KCNH2, KCNQ1,* and *KCNJ2).* The reason for this testing, even in the face of the majority of causative mutations being unknown, is primarily to determine the type of SQTS for both prognostic and therapeutic purposes.

Patients with congenital SQTS have very short atrial and ventricular refractory periods and ventricular fibrillation can be easily induced with programmed ventricular stimulation [31]. Consistent between LQTS and SQTS, an electrophysiology study to assess inducibility of ventricular tachycardia or ventricular fibrillation by programmed electrical stimulation is not necessary to establish a diagnosis.

Risk Stratification

Long QT Syndrome

Risk stratification of patients with LQTS plays a central role in guiding therapy after diagnosis. Accumulating data from the International LQTS Registry has facilitated a comprehensive analysis of risk factors for aborted cardiac arrest or SCD in multiple prespecified age groups [20, 32–35]. These analyses have consistently indicated that the phenotypic expression of LQTS is time dependent and age specific, warranting continuous risk assessment in affected patients.

Utilizing the data from the International LQTS Registry studies, patients with LQTS are risk stratified for the probability of a future cardiac event (syncope or SCD) primarily according to LQT genotype [13, 32, 34] (when identified), mutation location [35] (when identified), and QTc interval length [20, 32, 36], followed by sex [33, 34, 37], age [33, 34, 37], and number and type of events. A family history of SCD in a first-degree relative of genotype-positive LQT patients has not been shown to be a significant predictor of adverse outcomes in populations that are of mixed LQT genotype but predominately LQT1 [33].

Low risk patients (probability of first cardiac event <30%) include men or women with LQT1 and QTc <500 ms and men with LQT2 and QTc < 500 ms. Intermediate risk patients (probability of first cardiac event 30–49%) include women with LQT2 and QTc <500 ms, men with LQT3 and QTc <500 ms, and women with LQT3. High risk patients (probability of first cardiac event ≥50%) include men or women with LQT1 or LQT2 and QTc ≥500 ms and men with LQT3 and QTc ≥500 ms [14]. Adequate risk stratification, particularly in young asymptomatic genotype-positive patients, is very complex secondary to the morbidity of implantable cardioverter-defibrillator (ICD) therapy weighed against the risk of SCD.

Asymptomatic LQTS patients have a lower event rate per year or per decade than patients with a prior cardiac event [7, 33, 37, 38]. Patients with prior syncope have a much higher likelihood of future events including SCD [37, 38]. In early childhood, boys with LQT1 are more likely to suffer syncope or sudden death, but less likely than girls to have symptoms later in life [39]. This gender risk reversal has been recognized and reported in all patients with LQTS, where male patients with LQTS are at higher risk for events up to the age of 15 [37], after which women appear to be at greater risk [34, 39, 40]. Women with LQT2 appear to be at higher risk for cardiac arrest, syncope, and/or sudden death than males and remain at risk into adulthood [14, 41], while males with LQT3 are more likely to have events than are their female counterparts [14]. The increased risk of cardiac events in post-pubertal women ongoing through menopause supports a currently poorly understood hormonal contribution to abnormalities in ventricular repolarization and arrhythmogenesis in this population [32]. Overall, the number of deaths in patients with LQTS is greater in women than in men [42].

Short QT Syndrome
As most patients who are phenotype positive have currently unknown genetic mutations, the role of genetic testing is limited. Patients who present with the short QT phenotype (short QT on ECG and symptoms) should be tested for the three most common mutations noted above. Patients who test positive for KCNJ2 are at low risk for future adverse events and can forgo further therapy, whereas those who test positive for KCNQ1 are more likely to experience arrhythmic events and should be considered for more aggressive, device-based therapy [43]. Given that congenital short QT syndrome is a relatively newly recognized clinical syndrome, beyond such gene-specific risk stratification, little in the way of data is available regarding clinical risk stratification. As a rough rule of thumb, however, patients with SQTS who have suffered syncope are at high risk for recurrent events and should be considered for aggressive medical and device therapy.

Treatment Approach

The treatment scheme is similar for both of these congenital arrhythmias, despite their different pathophysiology and genetic origin. High risk LQTS patients, those post-cardiac arrest or with numerous arrhythmic syncopal episodes, and all SQTS patients should be treated aggressively with ICD placement. This is typically in addition to available medical therapy (beta-blockers for LQTS and quinidine for SQTS) to prevent future episodes. Intermediate or low risk LQTS patients are often managed medically and observed longitudinally for persistent symptoms.

Long QT Syndrome
Given the increasing prevalence of congenital LQTS and the associated risk of SCD, health care providers are likely to find themselves encountering challenging management decisions. The mainstay of treatment for all patients with LQTS is lifestyle modification and beta-blocker therapy [37, 44–46] with the implantation of an ICD when medical therapy fails or with a presenting cardiac arrest [47]. These three more common and other less frequently utilized therapies for LQTS are discussed below.

Lifestyle Modification

Competitive sports or extreme exertion should be avoided by all patients with congenital LQTS [48]. Possible exceptions may include golf, curling, cricket, billiards, or bowling [48]. Even noncompetitive swimming, especially for LQT1 patients, must be limited and if performed should be done so under close supervision. Patients with LQT2 should avoid startling acoustic stimulation such as alarm clocks [3]. Electrolyte losses due to vomiting, diarrhea, or excessive sweating should be replaced in order to avoid hypokalemia and hypomagnesemia that may exacerbate prolongation of the QT interval. In addition, LQTS patients must avoid medications known to prolong the QT interval with particular attention paid to antibiotic, antiemetic, antiepileptic, antiarrhythmic, antipsychotic, and antidepressant medication classes (see www.qtdrugs.org).

Beta-Blockers

The mainstay of medical therapy for all patients with LQTS involves beta-blocker therapy [49]. As ventricular arrhythmias may arise during a state of high adrenergic tone and increase the occurrence of after-depolarizations, beta-blockers are used to blunt adrenergic stimulation. Beta-blockers themselves do not shorten the QT interval; rather, they act to minimize the risk of triggered activity through modulation of the cardiovascular adrenergic tone. Unfortunately, beta-blockers provide less protection to patients with LQT3, as has been described pre-

viously [50]. Even though no randomized controlled trials exist, observational data suggest a strong mortality benefit with beta-blocker therapy [49]. The efficacy of beta-blockade may be assessed with exercise tolerance testing to ensure that there is blunting of the heart rate response during exertion.

Implantable Cardioverter-Defibrillator

Use of an ICD in conjunction with beta-blockers has proven invaluable in the treatment of patients with LQTS suffering ongoing symptoms despite beta-blocker therapy [47, 51, 52]. ICDs are now considered first line therapy for patients who have had a previous cardiac arrest, those with recurrent arrhythmic syncope despite beta-blocker therapy [52, 53], patients who cannot tolerate beta-blockers or in whom beta-blockers are contraindicated, and high risk patients (QTc >500 ms in men/women with LQT1 and LQT2 and in men with LQT3) and patients with a QTc >550 ms.

Sympathectomy

Left cervicothoracic sympathectomy involves surgical resection of the lower half of the left stellate ganglion along with several other thoracic ganglia in an attempt to denervate the heart [54]. This procedure, which can now be performed in a minimally invasive manner [34], remains an option for patients intolerant of beta-blockers, those with recurrent cardiac events on beta-blockers, patients receiving multiple ICD shocks, and patients in whom an ICD implant is not feasible due to either physical or psychosocial limitations.

Permanent Pacemaker Implant

When combined with beta-blockers, ventricular pacing, which prevents bradycardia, may facilitate the titration of beta-blockers to more effective antiarrhythmic doses and can also serve to prevent pause-dependent torsades de pointes [55, 56]. However, no randomized study exists comparing the efficacy of pacemakers combined with beta-blockers to ICDs in preventing symptoms in patients with LQTS and this approach is only utilized in conjunction with ICD implantation.

Emerging Therapy

Ranolazine is an antianginal agent that is approved for the treatment of chronic ischemic chest pain [57]. Ranolazine has several effects on ion channels, but its primary effect is reduction of the late sodium current (late Ina), a depolarizing current which contributes to action potential prolongation [57]. Preliminary studies have shown significant QT interval shortening when ranolazine is given as an infusion to patients with LQT3 [58]. Ranolazine is not currently approved for the treatment of LQTS and studies of ranolazine in patients with LQTS are ongoing.

Flecainide is a class IC antiarrhythmic drug with potent sodium channel-blocking properties. Patients with LQT3 mutations have an abnormal sodium channel allowing an inward current to persist long into the plateau phase of the action potential, thereby prolonging the QT interval. In these patients, flecainide has been shown to shorten and even normalize the QT interval [59]. However, flecainide may increase the risk of SCD in patients with overlapping LQT3 and Brugada syndrome, making its routine use not recommended [60]. Furthermore, there is no evidence that flecainide or other sodium channel blockers reduce mortality in LQT3.

Short QT Syndrome
Patients with congenital SQTS have a very high risk of sudden death and for this reason ICD implantation has been recommended as first line therapy [6, 31, 43]. However, it should be stressed that secondary to our limited experience with SQTS the therapeutic options are limited beyond ICD implants. Of course, device implantation in young patients presents numerous technical as well as psychosocial issues that may make device implantation prohibitive. Genetic testing, when positive for known SQTS mutations, can provide further guidance regarding this often difficult decision. Asymptomatic patients with SQTS who have a positive KCNJ2 mutation are less likely to have adverse events and may forego ICD implants, whereas those who test positive for KCNH2 are more likely to experience arrhythmic events and should receive more aggressive, device-based therapy [18, 19, 61]. As the role of genetic information is usually limited (as few patients are genotype positive for the described mutations) the decision to pursue ICD implantation often remains difficult for clinicians and families.

KCNH2-positive patients may also be considered for antiarrhythmic therapy with quinidine, as originally described by Gaita et al. [43]; it normalized the QT interval

and rendered VT/VF noninducible at EP study after ICD implantation. In contrast, patients who were not KCNH2 positive did not experience normalization of the QT interval or loss of ventricular arrhythmia inducibility.

Conclusion

Patients with congenital LQTS and SQTS are at risk for sudden death. Modern genomics has shed light on the mechanism of arrhythmia induction in these patients and has allowed for their further risk stratification. As the number of described mutations increases for both syndromes (particularly for SQTS) it may be possible to identify responsible mutations in all phenotype-positive patients, improving risk stratification and simplifying therapeutic decision making. Accurate diagnosis and institution of effective contemporary medical and/or device therapy can favorably improve outcomes in these patients.

Conflict of Interest

The authors have nothing to disclose.

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