An Overview of Long QT Syndrome

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INTRODUCTION

Long QT syndrome (LQTS) is characterized by QT prolongation with repetitive episodes of rapid, polymorphic ventricular tachycardia with a phasic continuous alteration of the QRS morphology, termed as *torsades de pointes (TdP)* (Fig. 1). The term "torsades de pointes" (twisting of the points) was coined in 1966 by Dessertenne, who used it to describe the pause-dependent polymorphic ventricular tachycardia that he observed in an elderly patient with syncope, heart block, and marked QT prolongation.[1]

Long QT syndrome can be congenital or acquired. The congenital LQTS has predominantly two variants; Jervell and Lange-Nielsen (J-L-N) syndrome associated with congenital sensori-neural deafness and an autosomal recessive inheritance[2] and Romano-Ward (R-W) syndrome without deafness and an autosomal dominant inheritance.[3-4]

HISTORICAL ASPECTS

The first LQTS family was reported in 1957, when Jervell and Lange-Nielsen described the J-L-N syndrome in several families of Norwegian origin. In 1963, Romano and Ward described the R-W syndrome. Since 1991 (post-genomic era), seven LQTS genes have been discovered and more than 300 mutations have been identified to account for approximately 70% of patients affected. Moss and Donald performed left cardiac sympathetic denervation for the first time in 1971 in an LQTS patient refractory to the conventional antiarrhythmic therapy.

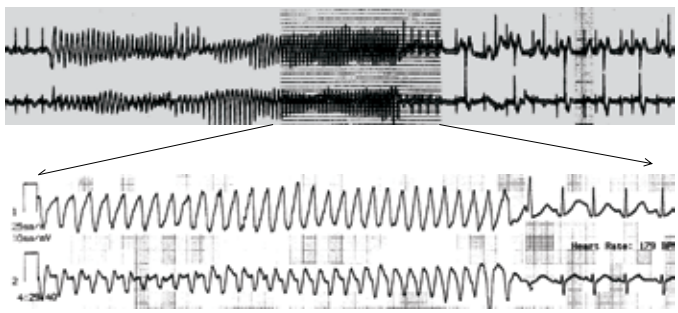

Fig. 1a: Holter trace showing polymorphic ventricular tachycardia- torsades de pointes with prolonged QT interval

EPIDEMIOLOGY

The incidence of congenital LQTS is 1:10,000 to 1:15,000. About 20% of symptomatic patients with history of syncope and who are untreated die within a year and mortality rises to 50% over 10 years.[5] It is alarming to know that 5-10% of gene carriers have no QT prolongation[6] and about 5% of family members of congenital LQTS experience life-threatening arrhythmias despite normal QT intervals.[7] Among LQTS patients, the risk of cardiac events was higher in males until puberty and higher in females during adulthood.[8] This finding supports the original observation made by Hashiba, showing the regression of LQTS phenotypic manifestations, both QT_c duration and cardiac events, among affected males after puberty. Age- and sex-dependent differences in clinical manifestations are also present among patients with LQTS-gene mutations. The QT_c is known to be age- and sex-dependent in the normal population, with lower values in adult males.[9] Among patients with identified LQTS genotypes, adult males had shorter QT_c duration than adult females and children.[10]

PATHOPHYSIOLOGY

There have been two hypotheses forwarded to explain the pathogenesis of LQTS.[11] One hypothesis suggests a sympathetic imbalance with a decrease in right cardiac sympathetic activity and higher than normal left sympathetic activity. The lower than normal heart rates in LQTS patients with decreased chronotropic response on exercise played a major role in development of this hypothesis. The syncopal episodes are triggered by sudden sympathetic discharges, which are mostly mediated by the left stellate ganglion. Another, more recent and well-accepted hypothesis suggests an intra-cardiac abnormality with dysfunction of cardiac ion channels thereby producing an intrinsic abnormality in the mechanisms responsible for cardiac repolarization.

The arrhythmia in LQTS is due to action potential prolongation that is explained by early after-depolarizations (EAD).[12] TdP is thus, a triggered rhythm due to EAD in both congenital and acquired forms of LQTS. Although the initiation of TdP can be explained with EAD, reentry could be possibly responsible for sustained arrhythmia. EAD results in prolongation of the action potential, which is a result of either reduction in normal

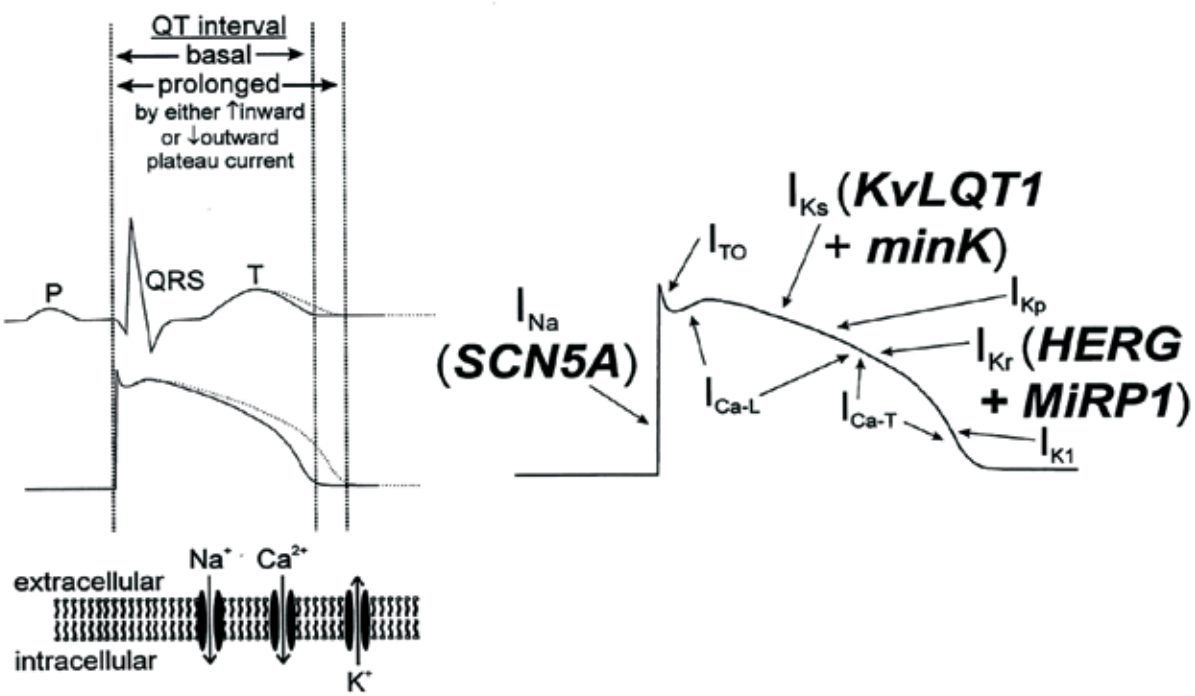

Fig. 2 : Ionic basis explaining the QT prolongation in different genotypes of LQTS

repolarizing (K^+) current or an abnormal prolongation of inward current carried by Na^+ or Ca^+ channels during the plateau phase. Conditions like hypokalemia, hypomagnesaemia and catecholamines are known to cause EADs.

MOLECULAR BIOLOGY OF LQTS

It has been well established that congenital LQTS is caused by mutations in some genes that encode for cardiac ion channels (Fig. 2). Till date, seven genotypes have been recognized, which also influence the clinical course of the syndrome. Also, the different genotypes exhibit some distinctive T wave patterns (Fig. 3) on ECG, which can be used to clinically identify the genotypes[13] (Table 1).

1. LQT1- This is the commonest type seen accounting for 50-60% of LQTS cases and is caused by mutations in the KvLQT1 gene on chromosome 11.[14] This gene encodes an abnormal potassium channel protein (D subunit). There is reduction of the slow component of the delayed rectifier potassium current I_{ks}. Homozygous mutations of KvLQT1 appear to cause the J-L-N syndrome, and KvLQT1 has been shown in mice to influence the normal development of the inner ear. Thus, the cardiac phenotype (QT prolongation) of the J-L-N syndrome is inherited as a dominant trait, whereas deafness is inherited as a recessive trait. LQT1 has also been associated with the most favorable response to E-blocker therapy.[15] The ECG characteristically shows a broad-based T-wave.
2. LQT2- This type is caused by mutation in the HERG gene on chromosome 7.[16] This is the second most common mutated gene in LQTS. This gene encodes for the D subunit of a potassium channel that carries the phase 3 rapidly activating delayed rectifier potassium current (I_{kr} current). Low amplitude bifid T waves are seen on the ECG.
3. LQT3- Results from mutation in the SCN5A gene on chromosome 3 that encodes for the sodium channel protein.[17] The mutation causes the incomplete inactivation of the sodium inflow thereby allowing continued sodium entry into the myocardial cell during repolarization. These patients have a distinctive, late-appearing T wave.
4. LQT4- Is caused by mutations in Ankyrin-B gene on chromosome 4.[18] This affects the sodium channel and also alters calcium signaling. These patients have marked sinus bradycardia with sinus node dysfunction and atrial arrhythmias, unlike the other LQTS patients. The ECG shows pronounced U waves, distinct from the T waves.
5. LQT5- Is caused by mutations in KCNE1 (also called minK) on chromosome 21. This type accounts for less than 3% of the LQTS population. *KCNE1* encodes the E subunit of the potassium channel, which, combined with the alpha subunit encoded by KvLQT1, reduces the current of the slowly activating and delayed inwardly rectifying, I_{ks} (repolarizing) potassium channel.[19] Just as in LQT1, homozygous mutations in KCNE1 can result in congenital deafness, J-L-N syndrome.
6. LQT6- Is quite rare and caused by mutations in KCNE2 (or MiRP1) on chromosome 21. This gene along with the HERG gene affects I_{kr} and decreases the repolarizing potassium current.[20]
7. LQT7- This is caused by mutations in KCNJ2, which encodes the inward rectifier K^+ channel I_{kr}2.1. The mutation results in a rare, inherited disorder, called Andersen syndrome (AS), which is characterized by periodic paralysis, long QT (LQT) with ventricular arrhythmias, and skeletal developmental abnormalities.[21] Long QT is the primary cardiac manifestation, present in 71% of KCNJ2 mutation carriers, with ventricular arrhythmias present

in 64%. Using simulation techniques, it was observed that a reduction in $I_{kr}2.1$ prolongs the terminal phase of the cardiac action potential, and in the setting of reduced extracellular K^+, induces Na^+/Ca^{2+} exchanger–dependent delayed after depolarization's and spontaneous arrhythmias. These findings suggest that the substrate for arrhythmia susceptibility in AS is distinct from the other forms of inherited LQT syndrome.

DIAGNOSTIC FEATURES

Clinical presentation

The commonest presentation of LQTS is syncope or cardiac arrest precipitated by strong emotions like fright or anger or physical stress, especially where there is sudden increase in sympathetic activity. Sudden awakening, especially with an auditory stimulus, also triggers the syncope. Swimming can also precipitate syncope. Syncope on exertion in pediatric patients should be considered malignant until proven otherwise Unexplained seizures have been associated with LQTS and have often led to misdiagnosis of epilepsy. A higher incidence of syncope has been seen with menstruation and post-partum period. In LQT2 and LQT3, sporadic cases of cardiac arrest occurring exclusively at rest or during sleep have been observed.

The syncopal episodes result from TdP, which can degenerate into ventricular fibrillation (VF). The family screening can often detect prolongation of the QT interval, with history of fainting or sudden unexpected young deaths within the family.

The genotype of the long QT syndrome influences the clinical course and is an independent predictor of first cardiac event. LQT1 and LQT2 have a significantly higher likelihood of cardiac events as compared to LQT3 patients. Also, younger age of onset and increased recurrence of cardiac events is observed in LQT1 and LQT2. However, the lethality of the cardiac event i.e. the risk of death during a cardiac event is significantly higher in LQT3.

Electrocardiographic (ECG) abnormalities:

1. *Prolongation of the corrected QT interval (QTc)*: In most of the patients, QTc, as calculated with Bazett's formula, is more than 460 msec; in males more than 450 msec and in females more than 470 msec. The lead II is considered to be the best to for QTc measurement, showing to have longest QT interval in 82% of patients. The degree of QT prolongation is variable and the occurrence of more malignant symptoms is more associated with longer QT prolongations (QTc in excess of 600 msec).
2. *T wave abnormalities*:
   a. *T wave morphology*- In LQTS, along with duration of the repolarization, its morphology is also altered. The T wave may be biphasic or notched in the most typical presentation suggesting the regional differences in the time course of ventricular repolarization. These findings are best seen in the precordial leads. The T wave morphology may be characteristic of underlying genotype. It has been observed in some studies that the appearance of notched T waves in the recovery phase of exercise is markedly more frequent among LQTS patients than healthy controls. T wave notches may be related to the presence of sub-threshold early after depolarizations. This can explain the relation between the notches and the higher risk of developing cardiac arrhythmias.

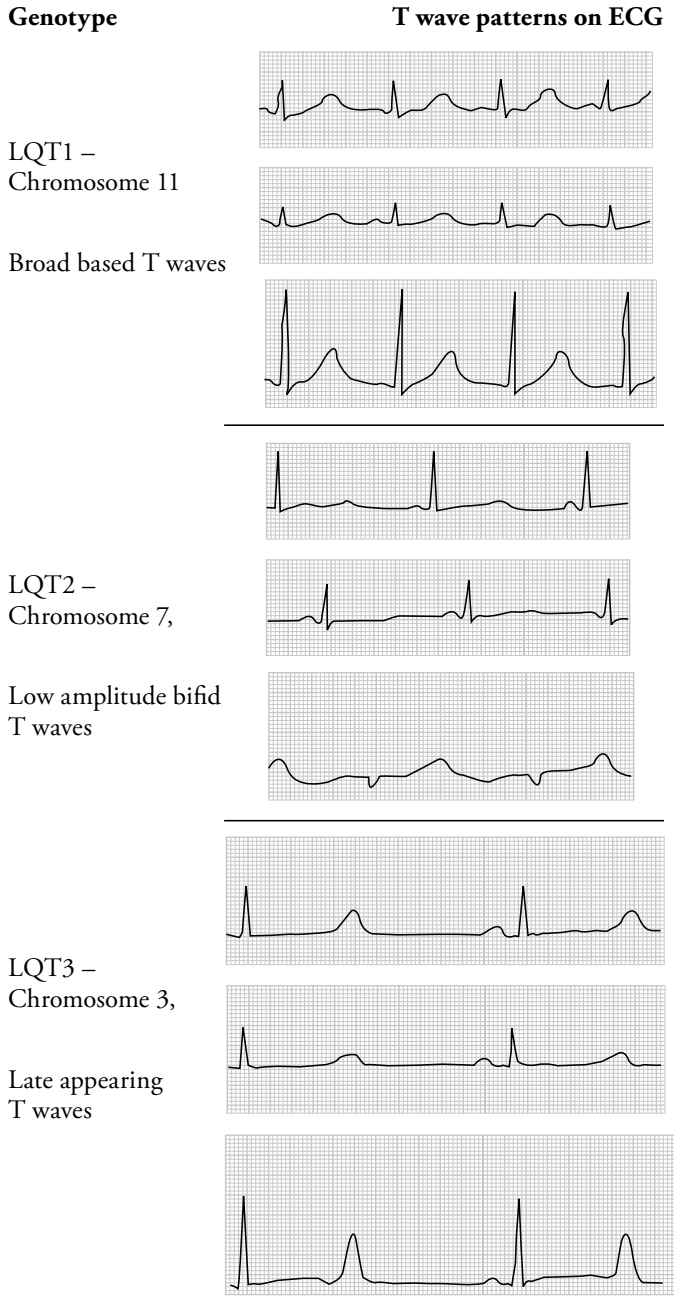

Fig. 3 : Distinctive T wave patterns of three genotypes of LQTS as seen on ECG

   b. *T wave alternans* (Fig. 4) : Beat-to-beat alternation of T waves,[22] in polarity or amplitude represents the second characteristic electrocardiographic feature of LQTS. It may be seen at rest briefly, but most often it appears during periods of emotional or physical stress and may precede TdP. Other techniques like signal averaged ECG and recently, spectral analysis may detect 'micro' or 'occult' T-wave alternans, which is not seen on routine ECG. T wave alternans is regarded as a marker

Table 1 : Different Characteristics of LQTS Genotypes

LQTS type	Gene and chromosome	Cardiac ion channel involved	ECG features	Triggers for TdP	Treatment
LQT1	KvLQT1, chromosome 11	D subunit of potassium channel- reduction in I_{ks} current	Broad based T waves	Strong emotions or activity like swimming	Beta-blockers
LQT2	HERG gene, chromosome 7	D subunit of a potassium channel- reduction in I_{kr} current	Low amplitude bifid T waves	More at rest or during sleep, noise stimulus	Pacemaker, beta-blocker less effective. K^+ supplements / K^+ sparing agents
LQT3	SCNA5 gene, chromosome 3	Sodium channel	Late appearing T waves	More at rest or during sleep	ICD. Sodium channel blockers like mexilitine
LQT4	Ankyrin-B gene, chromosome 4	Sodium channel, sodium calcium exchanger, alters calcium signaling	Sinus node dysfunction and atrial fibrillation; pronounced U waves distinct from T waves.	-	-
LQT5	KCNE1 or minK gene, chromosome 21	E subunit of the potassium channel	-	-	-
LQT6	KCNE2 or MiRP1, chromosome 21	Potassium channel	-	Certain drugs, stress	-
LQT7	KCNJ2	Inward rectifier potassium current	-	-	-

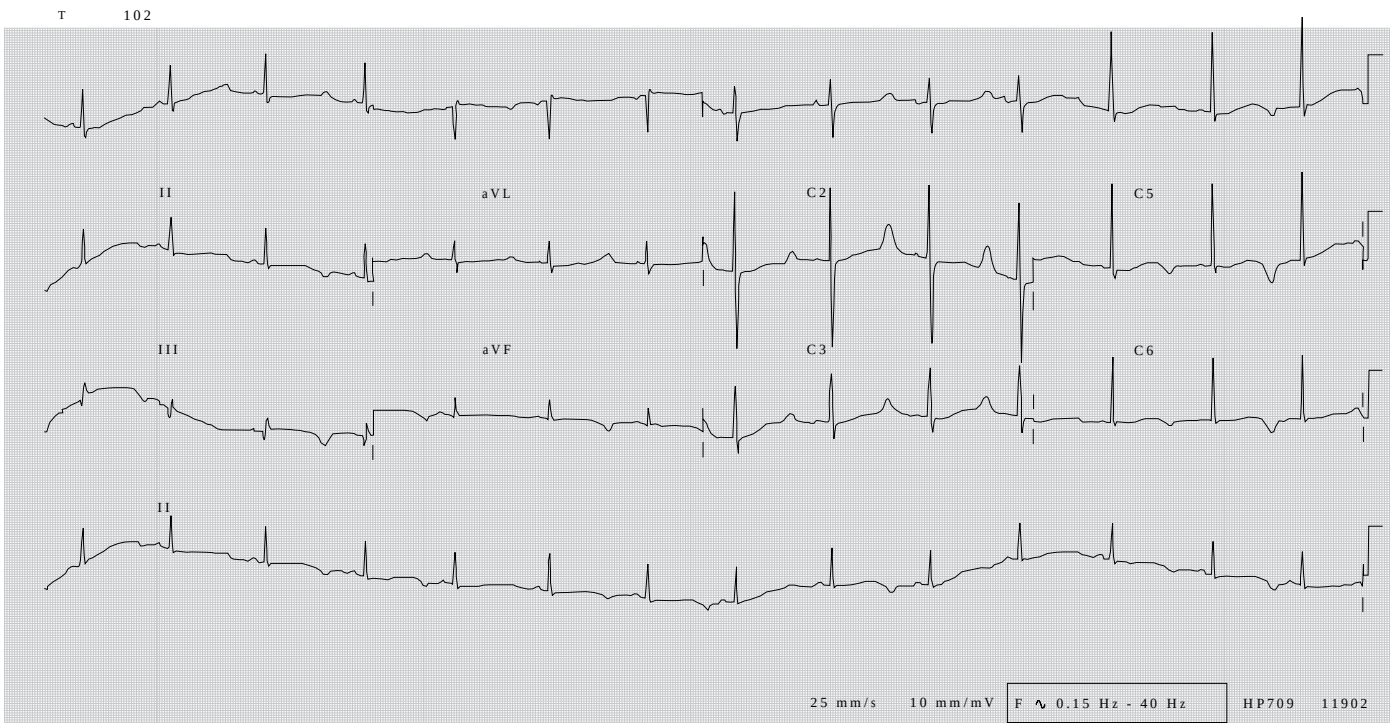

Fig. 4: A 12 lead ECG showing QT prolongation with T wave alternans, most prominent in lead II.

of major electrical instability and it identifies patients at particularly high risk.

In some LQTS patients, U waves may be more exaggerated in addition to T wave abnormalities.

3. *QT dispersion:* LQTS patients have a marked heterogeneity in the repolarization of different regions of the myocardium, which can be reflected by measurement of QT dispersion. It is the difference between the shortest and the longest QT in a simultaneously acquired and displayed 12 lead ECG. A QT dispersion of 60 ms or more is considered significant.
4. *Bradycardia:* A lower than normal heart rate is observed in most patients, especially striking in children. Also, on

exercise, lower heart rates are reached as compared the normal population. In addition to this, LQTS patients have sudden pauses, not related to sinus arrhythmia and in some atrio-ventricular block is also observed. These pauses are often followed by notch in the T wave and it is these notches that start off the repetitive ventricular beats and initiate the arrhythmias. Thus, these pauses often precede the TdP.

Echocardiographic abnormalities

Primarily two abnormalities are seen as evident on M-mode of the left ventricle: an increased rate of thickening in the early phase of contraction (the time to reach half of maximal systolic contraction as percent of cardiac cycle) and the presence of slow movement in the late thickened phase before rapid relaxation with a plateau morphology which is sometimes associated with a second peak.[23] These abnormalities are more observed in symptomatic patients. These are due to an abnormal increase in the intracellular calcium concentration before the completion of relaxation and this may be related to EAD and the contraction abnormality would be the mechanical equivalent of the EAD. These abnormities are seen to disappear by verapamil.[24]

Diagnostic criteria

A diagnostic criteria has been proposed for LQTS with points assigned to different findings.

		Points
ECG findings:		
1.	QTc - > 480 msec	3
	460-470 msec	2
	450 msec (male)	1
2.	Torsades de pointes	2
3.	T wave alternans	1
4.	Notched T wave in three leads	1
5.	Low heart rate for age (Below 2nd percentile for the age)	0.5
Clinical History		
1.	Syncope - With stress	2
	- Without stress	1
2.	Congenital deafness	0.5
Family history		
1.	Family members with definite LQTS	1
2.	Unexplained sudden cardiac death below 30 years of age among immediate family members	0.5

A score of less than 1 point suggests low probability of LQTS, 2-3 points suggests intermediate probability of LQTS and more than 4 points suggest high probability of LQTS.

MANAGEMENT

The approach to a patient with congenital LQTS should begin with risk stratification of the patient. There would be two basic categories of the LQTS patients: symptomatic and asymptomatic.

Symptomatic patients

A sudden increase in sympathetic activity usually mediated by the left cardiac sympathetic nerves is the commonest triggering factor for the episodes of life-threatening arrhythmias of LQTS. Thus, logically, pharmacological or surgical anti-adrenergic therapy or both should be mainstay in the treatment of symptomatic patients with LQTS.

Beta-adrenergic blockade is the first choice in the therapy of symptomatic LQTS patients, unless it is contraindicated for patients with asthma or diabetes. Propranolol is the most widely used drug in a daily dosage of 4 to 10 mg/kg. The dose of beta-blockers should be large enough to demonstrate competitive blockade on exercise testing with the heart rate being limited to 120-130/min. The impairment of I_{ks} current makes these patients sensitive to catecholamines and responsive to beta-blockade.

The analysis by the International Registry of 869 patients[11] treated with beta-blockers, which included 315 asymptomatic patients threw some light on the concepts that although beta-blockers reduce the incidence of arrhythmic events significantly, not all patients are fully protected. In case of patients with syncope as the presenting symptom prior to the initiation of beta-blocker therapy, the recurrence of syncope is not rare (approximately 30%), but the probability of cardiac arrest or death is only 3%. However, in case of patients presenting with cardiac arrest, the probability of a new cardiac arrest or death despite beta-blockers is 13%. Thus, beta-blockers at full dose should be the first choice in patients presenting with syncope and high success rates could be achieved as regards the prevention of life-threatening events, whereas patients with cardiac arrest are at a much higher risk and so ICD is advisable along with beta-blockers.

Some patients like the ones with LQT3 cannot tolerate beta-blockers because of excessive bradycardia or the low heart rate favors EAD induced TdP in them. In such patients, combination of beta-blockers and cardiac pacing is advisable. Beta-blockers can sometimes be combined with class 1B anti-arrhythmic drugs like mexilitine.

Left Cardiac Sympathetic Denervation (LCSD) is a surgical method of anti-adrenergic therapy. It involves removal of first four to five thoracic ganglia. Horner's syndrome can be avoided by preserving the cephalic portion of the left stellate ganglion.[25] Patients who are unresponsive to or cannot tolerate full dose beta-blocker therapy should undergo LCSD. The lethal arrhythmias are prevented by LCSD by modifying the substrate in addition to removal of trigger. This modality is now occasionally used in infants and in patients refractory to other forms of therapy.

Full dose beta-blockade and LCSD prevent sudden cardiac death in 96% to 97% of symptomatic patients.

Cardiac Pacing is never indicated as a sole therapy in LQTS. It is most often used as an adjuvant to beta-blocking therapy (Figure 5). Pacemaker is also indicated in LQTS with atrioventricular block and in cases of pause dependent malignant arrhythmias and in ones occurring during sleep or rest.

Implantable cardioverter defibrillator (ICD) is indicated when i) there is recurrence of syncope despite full dose beta-blocker and LCSD, ii) cardiac arrest requiring resuscitation occurs during beta-blocker therapy and iii) the first event is a cardiac arrest. The ICD does not prevent the occurrence of malignant arrhythmias, but offers protection of life in the event of such happenings. However, it should be remembered that most of the

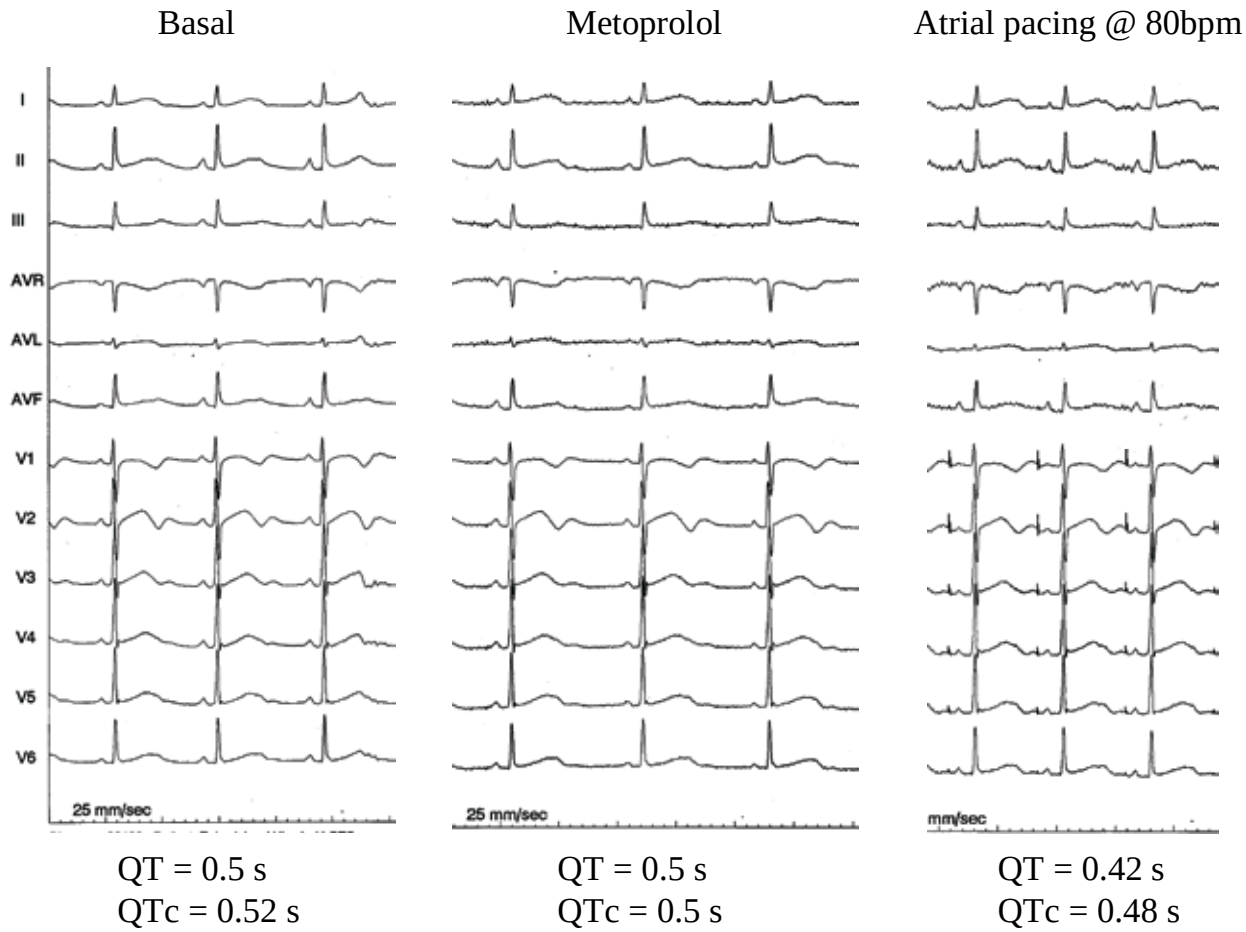

Fig. 5 : Panel on the left shows a 12 lead ECG showing prolonged QTc interval (0.52 sec). The middle panel shows a 12 lead ECG of the same patient on metoprolol with no significant change in the QT interval. However, the panel to the right shows shortening of the QT interval in the same patient after atrial pacing.

TdPs are frequently self-terminating in LQTS patients and the ICD discharges, on the contrary, can worsen the arrhythmias, due to increased catecholamine release triggered by pain and fear following an ICD discharge, thereby producing a vicious circle. So, it is essential to use the ICD judiciously weighing the pros and cons and also, adjusting the settings so as to avoid delivering immediate shocks, in view of the high possibility of spontaneous termination of TdP.

Asymptomatic patients

Asymptomatic patient with a prolonged QT interval and ones who are siblings or close relatives of fully symptomatic patients always carry a risk, even if remote, of a life-threatening arrhythmia, the risk being lower for LQT1 patients and higher among patients with LQT3. It is advisable to start all patients diagnosed with LQTS on beta-blocker therapy. Though apparently, this would lead to unnecessary treatment of many patients, it will prevent significant number of sudden cardiac deaths occurring during the first arrhythmic episode, the incidence of which is approximately 7% to 9%. The asymptomatic patients who are at a high risk and must be started on therapy are: i) Patients with congenital deafness, ii) neonates and infants in the first year of life- QT prolongation during the first year of life represents a major risk factor for sudden infant death syndrome, iii) siblings of patients who have died suddenly during some acute emotional situation, iv) patients with documented evidence of T wave alternans, which indicates high electrical instability, v) patients with QTc exceeding 600msec and vi) if a treatment is requested by the patient himself, after he has been explained the condition thoroughly.

Besides the above treatment, the family members need to be instructed in cardiopulmonary resuscitation, especially thump cardioversion and also given the list of all the drugs that should be avoided in long QT syndrome (Table 2).

Similarly, the knowledge of the specific genetic mutations can certainly provide clues to more focused therapeutic approaches. These have not been entirely established and are still in experimental stages. For example, in patients with SCN5A mutations (LQT3), sodium channel blocker, mexilitine can prove efficacious. Also, since in LQT3, the exercise stress test produces a significant shortening of the QT interval and quite a few TdP episodes occur during sleep, during bradycardia, these patients need not be advised restriction of physical activity and would benefit from pacemaker more than LQT1 and LQT2 patients. In patients with mutations in HERG gene (LQT2), increasing extracellular potassium should be tested using oral potassium

Table 2 : Causes of Acquired Long QT Syndrome

I. Drugs

a. Antiarrhythmics

Class IA: Quinidine,
Procainamide,
Disopyramide

Class III: Sotalol, Dofetilide, Ibutilide, Bretylium, N-acetyl procainamide, Amiodarone (rare)

b. Other cardiac drugs

Bepridil
Probucol

c. Antibiotics

Erythromycin, Clindamycin, Clarithromycin, Quinolones, especially sparfloxacin, Trimethoprim- sulfamethoxazole, Chloroquine, Pentamidine, Amantadine, Halofantrine Misoridazine

d. Antifungals

Itraconazole, Ketoconazole Fluconazole

e. Psychotropics

Antidepressants: Tricyclics (i.e., Amitriptyline, Desipramine), Tetracyclics, Fluvoxamine Haloperidol, Droperidol, Thiothixene, Doxepin, Risperidone, Phenothiazines, Pimozide, Thioridazine

f. Antihistamines

Astemizole, Terfenadine, Diphenhydramine

g. Gastrointestinal

Cisapride, Domperidone

h. Diuretics

Indapamide

i. Others

Levomethadyl, Chlorpromazine, Glibenclamide, Organophosphate insecticides

II. Metabolic factors

Hypokalemia, Hypomagnesemia, Hypocalcemia

III. Bradyarrhythmias

Sinus bradycardia, Atrioventricular block

IV. Cerebrovascular abnormalities

Intracranial hemorrhage, Subarachnoid hemorrhage, Stroke

V. Cardiac abnormalities

Congestive heart failure, Myocardial infarction, Myocarditis, LVH

VI. Miscellaneous

High protein liquid diets, Autonomic neuropathy, Human immunodeficiency virus disease.

supplements along with potassium sparing agents. Potassium channel openers (nicorandil) are also being tested

Identification of asymptomatic gene carriers with normal phenotype i.e. normal QT interval is essential, since such patients can be advised life-style modifications avoiding stressful conditions, strenuous exercises, certain drugs and taking precautions during anesthesia for surgery. Parental planning can also be done with this information.

ACQUIRED LQTS

Extrinsic factors like drugs (Table 2) or some metabolic factors result in QT interval prolongation leading to the life-threatening ventricular tachyarrhythmias i.e. TdP.

It has been observed that newborns of mothers positive for anti-Ro/SSA auto-antibodies with maternally acquired anti-Ro/SSA antibodies may develop prolongation of the QTc interval and these ECG abnormalities disappeared along with the acquired maternal auto-antibodies during the first year, which suggests a direct, reversible electrophysiologic effect of anti-Ro/SSA antibodies on the ventricular repolarization. Similarly, adults with anti-Ro/SSA auto-antibodies also show a high risk of prolonged QTc and life threatening arrhythmias. Morbid obesity is also associated with an acquired prolongation of the QTc interval and weight loss can significantly reduce the incidence of malignant arrhythmias. Occasionally, acute pulmonary embolism can present with reversible QT prolongation and deep T wave inversions. There have been isolated case reports where acquired LQTS was seen to be associated with primary hypothyroidism.

Pathophysiology

A significant number of drug-induced TdP is now considered to be due to form-fruste mutation in the LQTS genes and some of the patients might be carriers of silent mutation.[26]

Acquired LQTS is usually associated with pharmacological inhibition of cardiac potassium channels, where several drugs preferentially block the rapid component of delayed rectifier K^+ current (I_{Kr}). Subclinical mutations in the LQTS-related gene *SCN5A* that encodes for sodium channel may also predispose certain individuals to drug-induced cardiac arrhythmias. In the presence of risk factors such as female gender, slow heart rate, and hypokalemia, these drugs can induce TdP. Although all the drugs act by blocking the I_{Kr}, the extent of QT prolongation and TdP varies in individuals depending on the repolarization reserve.

The polymorphic VT in acquired LQTS commonly occurs after short-long-short QRS complex sequence and is pause dependent. The mechanism of TdP here is triggered activity with EADs.

Management

A patient presenting with TdP who is hemodynamically unstable should be immediately cardioverted with escalating energies of DC shocks. Once a sinus rhythm has been established, the underlying electrolyte abnormalities should be corrected along with the withdrawal of the offending or precipitating agent. IV magnesium has a very important role to play in the management of acquired LQTS to convert the TdP into a sinus rhythm and to prevent the recurrence. An initial dose of 2 g bolus of magnesium sulphate 50% can establish a sinus rhythm in many, but a repeat bolus after 5-15 minutes should be instituted if required, followed by an infusion at a rate of 1-4 g/hour. IV lidocaine may be used along with or if magnesium fails in a dose of 1.5 mg/kg bolus followed by infusion of 1-4 mg /min. Both magnesium and lidocaine suppress the EADs and thus help in controlling the TdP. Temporary atrial or ventricular pacing, IV isoproterenol can be used to increase the heart rate, but cautiously. In case of patients who present with recurrent TdP, an ICD implantation is worth considering.

CONCLUSION

Long QT syndrome, congenital and acquired, is a life-threatening cardiac electrical disease that needs to be recognized in a patient on an urgent basis, followed by aggressive risk stratification of the patient himself along with his family members, so as to institute

appropriate therapy as early as possible. The available modalities of treatment have a very high success rate in improving the morbidity and mortality associated with this disease, provided they are instituted judiciously. The genetic treatment, which is still in experimental stages, will certainly revolutionize the management of LQTS.

REFERENCES

1. Dessertenne F. La tachycardie ventriculaire a deux foyers opposes variables. *Arch Mal Coeur* 1966;59:263-272.
2. Jervell A, Lange-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval and sudden death. *Am Heart J* 1957;54:59-68.
3. Romano C, Gemme G, Pongiglione R. Aritmie cardiache rare in eta pediatrica. *Clin Pediatr*1963;45:656-683.
4. Ward OC. A new familial cardiac syndrome in children. *J Irish Med Assoc* 1964;54:103-106.
5. Moss AJ, Schwartz PJ, Crampton RS, et al. The Long QT syndrome: a prospective international study. *Circulation* 1985;71:17-21.
6. Vincent GM, Timothy KW, Leppert M, Keating M. The spectrum of symptoms and QT intervals in carriers of the gene for the long QT syndrome. *N Engl J Med* 1992;327:846-852.
7. Moss AJ, Schwartz PJ, Crampton RS, Tzivoni D, Locati EH, MacCluer J, et al. The long QT syndrome: prospective longitudinal study of 328 families. *Circulation* 1991; 84: 1136-1144.
8. EH Locati, W Zareba, AJ Moss, PJ Schwartz, GM Vincent, MH Lehmann, JA Towbin, SG Priori, C Napolitano, JL Robinson, M Andrews, K Timothy, and WJ Hall. Age- and Sex-Related Differences in Clinical Manifestations in Patients With Congenital Long-QT Syndrome: Findings From the International LQTS Registry. *Circulation* 1998;97:2237-2244.
9. Rautaharju PM, Zhou SH, Wong S, Calhoun HP, Berenson G, Prineas R, Davignon A. Sex differences in the evolution of electrocardiographic QT interval with age. *Can J Cardiol* 1992;8:690–695.
10. Lehmann MH, Timothy K, Frankovich D, Fromm B, Keating M, Locati E, Schwartz PJ, Moss AJ, Taggart RT, Towbin JA, Vincent GM. Age-sex influence on rate corrected QT interval and QT-heart rate relationship in families with genotypically characterized long QT syndrome. *J Am Coll Cardiol* 1997;29:93-99
11. Schwartz PJ, Locati EH, Napolitano C, Priori SG. The long QT syndrome. In: Zipes DP, Jalife J, eds. Cardiac Electrophysiology: From Cell to Bedside, 3rd ed. Philadelphia, Pa: WB Saunders Co; 2000:597-612.
12. Roden DM, Hoffman BF. Action potential prolongation and induction of abnormal automaticity by low quinidine concentrations in canine Purkinje fibers: relationship to potassium and cycle length. *Circ Res* 1985;56:857-867.
13. Zhang L, Timothy KW, Vincent GM, Lehmann MH, Fox J, Giuli LC, Shen J, Splawski I, Priori SG, Compton SJ, Yanowitz F, Benhorin J, Moss AJ, Schwartz PJ, Robinson JL, Wang Q, Zareba W, Keating MT, Towbin JA, Napolitano C, Medina A. (2000). Spectrum of ST-T-Wave Patterns and Repolarization Parameters in Congenital Long-QT Syndrome: ECG Findings Identify Genotypes. *Circulation* 2000;102:2849-2855
14. Wang Q, Curran ME, Splawski I, et al. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. *Nat Genet* 1996;12:17-23.
15. Moss AJ, Zareba W, Hall WJ, et al.: Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome**.** *Circulation* 2000;101**:**616-623.
16. Curran ME, Splawski I, Timothy KW, Vincent GM, Green ED, Keating MT. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. *Cell* 1995;80:795-803.
17. Wang Q, Shen J, Splawski I, et al. SCNA5 mutations cause an inherited cardiac arrhythmia, long QT syndrome. *Cell* 1995;80:805-11.
18. Schott JJ, Charpentier F, Peltier S, et al. Mapping of a gene for long QT syndrome to chromosome 4q25-27. *Am J Hum Genet* 1995;57:1114-22.
19. Barhanin J, Lesage F, Guillemare E, et al. KvLQT1 and IsK (mink) proteins associate to form the I_{ks} cardiac potassium current. *Nature* 1996;384:78-80.
20. Erica D Engelstein. Long QT Syndrome: A Preventable Cause of Sudden Death in Women. *Current Women's Health Reports* 2003;3**:**126–134 Current Science Inc. ISSN 1534–5874.
21. Tristani-Firouzi M, Jensen JL, Donaldson MR, *et al.*: Functional and clinical characterization of KCNJ2 mutations associated with LQT7 (Andersen syndrome). *J Clin Invest* 2002;110**:**381-388.
22. Schwartz PJ, Malliani A. Electrical alternation of the T-wave: clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long QT syndrome. *Am Heart J* 1975;89:45-50.
23. Nador F, Beria G, De Ferrari GM, Stramba-Badiale M, Locati EH, Lotto A, Schwartz PJ. Unsuspected echocardiographic abnormality in the long QT syndrome: diagnostic, prognostic, and pathogenetic implications. *Circulation* 1991;84:1530-1542.
24. De Ferrari GM, Nador F, Beria G, Sala S, Lotto A, Schwartz PJ. Effect of calcium channel block on the wall motion abnormality of the idiopathic long QT syndrome. *Circulation* 1994;89:2126-2132.
25. Schwartz PJ, Locati EH, Moss AJ, et al. Left cardiac sympathetic denervation in the therapy of congenital long QT syndrome: A worldwide report. *Circulation* 1991;84:503- 511.
26. Moss AJ, Schwartz PJ. Delayed repolarization (QT or QTU prolongation) and malignant ventricular arrhythmias. *Mod Concepts Cardiovasc Dis* 1982;51:85-90.