REVIEW

Brief Review of the Recently Described Short QT Syndrome and Other Cardiac Channelopathies

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There are many diseases related to ion-channel disorders, so-called "channelopathies." Hereditary short QT syndrome is a clinical-electrocardiographic entity with autosomal-dominant mode of transmission and it is the most recently described channelopathy. The syndrome may affect infants, children, or young adults with strong positive family background of sudden cardiac death. Short QT syndrome is characterized by short QT and heart-rate-corrected QTc intervals. It is frequently associated with tall-, peaked-, and narrow-based T waves that are reminiscent of the typical "desert tent" T waves of hyperkalemia. There is a high tendency for paroxysmal atrial fibrillation due to the heterogeneous abbreviation of action potential duration and refractoriness of atrial myocytes. The arrhythmia can also be induced by programmed electrical stimulation.

The safest treatment suggested is an implantable cardioverter defibrillator, though the possibilities of inappropriate shocks have caused some concern, especially in teenagers.

The ability of quinidine to prolong the QT interval has the potential to be an effective therapy for patients with short QT syndrome. This is particularly important in developing countries, where the implantable cardioverter-defibrillator therapy is not always available. Since these patients are at risk of sudden cardiac death from birth, and implantable cardioverter-defibrillator implantation has a lot of limitations in very young children, the utility of quinidine has to be evaluated further. Clinicians need to be aware of this deadly electrocardiographic (ECG) pattern as it portends a high risk of sudden cardiac death in otherwise healthy subjects with structurally normal hearts.

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congenital short QT syndrome; channelopathies; I_{KR} channels HERG; I_{KS} channels; sudden cardiac death

Genetic alterations may produce diverse defects on ion channels of cardiomyocytes, which are present in heritable cardiac arrhythmic syndromes. These alterations predispose affected individuals to cardiac arrhythmias and sudden cardiac death (SCD). The investigation of such "channelopathies" continues to yield remarkable insights into the molecular basis of cardiac excitability and cardiac arrhythmias. This concept is not restricted to genetic disorders; notably, changes in the expression or post-

translational modification of ion channels underlie the fatal arrhythmias associated with heart failure, and arrhythmias associated to functional ionic disturbances induced by some drugs with proarrhythmic effects, with or without genetic substrate.

CARDIAC CHANNELOPATHIES

The concept of channelopathies is related to a series of conditions, genetic or acquired, with the

clinical expression of some channelopathies occurring in the setting of heart failure. The genetic and drug-induced forms of this disorder occur without structural heart disease. Recognizing the pathophysiological defects in channelopathies provide the basis for new treatments, including tailored pharmacological and genetic therapies.¹

The channelopathies can affect sodium, potassium, (I_{to1} and delayed rectifier current I_{KS} , I_{KR} , I_{KUR} ,) chloride, calcium, cation transport mechanism of Na^+ - K^+ -ATPase, K^+ -ATPase; Na^+ / Ca^{+2} exchanger, acetyl choline-gated channels, and $InsP(3)R$ or inositol-1,4,5-trisphosphate receptors. These may lead to cardiovascular, neurological, ophthalmic, psychiatric, and other systemic disorders.²

The channelopathies can involve the sarcolemmal channels (external channelopathies), or the intracellular sarcoplasmic channels (internal channelopathies). They are now considered to be a collection of genetically distinct arrhythmogenic cardiac disorders resulting from mutations in fundamental cardiac ion channels that orchestrate the action potential (AP) of the human heart.

Cardiac Channelopathies Associated with Sudden Cardiac Death but without Structural Heart Disease

Sarcolemmal Channelopathies

- 1 Long QT syndrome (LQTS)³⁻¹³
- 2 Brugada syndrome¹⁴⁻¹⁷
- 3 Progressive cardiac conduction defect (PCCD), Lenègre disease; or "Idiopathic" progressive disease of His-Purkinje system¹⁸⁻²⁵
- 4 Idiopathic ventricular fibrillation (IVF)²⁶⁻³²
- 5 Mixed forms, or overlapping clinical phenotypes:
 - (a) Brugada syndrome associated with LQTS variant LQT3³³⁻³⁷
 - (b) Brugada syndrome associated with Progressive Cardiac Conduction Defect^{38,39}
 - (c) Brugada syndrome associated with sinus node dysfunction⁴⁰
 - (d) Brugada syndrome associated with atrial standstill⁴¹
- 6 Some sudden unexpected nocturnal death syndrome (SUNDS or SUDS)⁴²⁻⁴⁴
- 7 Some sudden infant death syndrome (SIDS)⁴⁵⁻⁴⁷
- 8 Congenital, hereditary, or familial short QT Syndrome (SQTS)⁴⁸

Endoplasmic Reticulum (Intracellular) Channelopathies

1. Catecholaminergic polymorphic ventricular tachycardia (CPVT) or familial polymorphic Ventricular tachycardia (FPVT)⁴⁹⁻⁵¹

Other Cardiac Channelopathies

1. Liddle's syndrome^{52,53}
2. High blood pressure blacks⁵⁴

LONG QT SYNDROME

Long QT syndrome (LQTS) is classified into two clinical groups, inherited (or hereditary) and acquired forms.

Hereditary LQTS

The different types of hereditary LQTS and their genetic background are displayed in Table 1.⁵⁵

Acquired LQTS

Several drugs and acquired clinical conditions are capable of inducing channelopathies. These entities are called acquired forms. An example is that produced by cocaine that has been reported to have two distinct clinical profiles of electrocardiographically documented life-threatening arrhythmias attributed to the drug. The first one is idioventricular rhythm that occurs in overdose situations, and appears to reflect excessive sodium channel block; it may respond to sodium bicarbonate. The second is "torsades de pointes" that occur in recreational users, who have underlying risks for this ventricular tachycardia (such as fully or partially expressed congenital LQTS), and reflects potassium channel blockade. These clinical observations can be explained by recent findings regarding the electrophysiologic effects of cocaine. Other patterns of severe arrhythmias due to cocaine may yet emerge.⁵⁶ There is a long list of drugs associated with acquired LQTS.

SHORT QT SYNDROME

Acquired Short QT Syndrome

The short QT syndrome can be induced by acidosis, alteration of the autonomic tone, drugs, electrolyte imbalance, and pathophysiologic states.

Table 1. Genetic Background of Inherited Forms of LQTS (Romano-Ward Syndrome) and (Jervell and Lange-Nielsen Syndrome)

LQTS Type	Chromosomal Locus	Mutated Gene	Ion Current Affected
LQT1	11p15.5	<i>KVLQT1 (KCNQ1)</i> (heterozygotes)	Potassium current (I_{Ks})
LQT2	7q35–36	<i>HERG</i>	Potassium current (I_{Kr})
LQT3	3p21–24	<i>SCN5A</i>	Sodium current (I_{Na})
LQT4	4q25–27	Ankyrin-B ^a or ankyrin 2 a non-ion channel protein(anchoring protein)	Ca (2+); Na/Ca exchanger; Na/K ATPase and InsP(3)R or inositol-1,4,5-trisphosphate receptors.Calcium signaling is altered.
LQT5	21q22.1–22.2	<i>KCNE1</i> (heterozygotes)	Potassium current (I_{Ks})
LQT6	21q22.1–22.2	<i>MiRP1</i>	Potassium current (I_{Kr})
LQT7	17	<i>KCNJ2</i>	Associated to Andersen's syndrome.
JLN	11p15.5	<i>KVLQT1 (KCNQ1)</i> (homozygotes)	Potassium current (I_{Ks})
JLN2	21q22.1–22.2	<i>KCNE1</i> (homozygotes)	Potassium current (I_{Ks})

^aHumans with ankyrin-B mutations display varying degrees of cardiac dysfunction including bradycardia, sinus arrhythmia, IVF, CPVT, and risk of SCD. However, a prolonged rate-corrected QT interval was not a consistent feature, indicating that ankyrin-B dysfunction represents a clinical entity distinct from classic long QT syndromes.⁵⁵

Hereditary Short QT Syndrome

The hereditary short QT Syndrome (SQTS) is a familial clinical-electrocardiographic entity with autosomal-dominant inheritance, and positive family history for SCD⁵⁷ characterized by a unique ECG repolarization pattern with constant and uniform short QT and QTc intervals and tall, peaked, pointed, narrow, and symmetrical T waves. The ECG can show left anterior fascicular block (LAFB). The ECG in our first case with SQTS is presented in Figure 1, with QTc of 312 ms when corrected for heart rate using the Framingham formula.⁵⁸

The hereditary SQTS is clinically characterized by major and minor cardiac events. The following ones are considered to be major: resuscitated cardiac arrest, syncope, and SCD; and the following are considered to be minor: palpitations and/or dizziness, nearly always secondary to bursts of paroxysmal atrial fibrillation (AF).

It is very important to recognize this ECG pattern, because it is related to a high risk of SCD in infants, children, and young adults, who are otherwise healthy individuals. The response to stress testing is a slight reduction of the QT interval during the physiological increase in heart rate. Short refractory periods and tendency for inducible atrial and ventricular fibrillation were seen in electrophysiological studies. Autopsy of fatal cases in this syndrome did not reveal any structural heart disease. Table 2^{48–59} shows the possible forms of SQTS.

GENETIC BACKGROUND

Recently, Ramon Brugada et al.⁴⁸ from the Masonic Medical Research Laboratory identified the first genetic defect in this new clinical entity. The study was the result of a collaborative effort among researchers in Europe and the United States. The authors detected a missense mutation resulting in an amino acid change (N588K) in the S5-P loop region of the outwardly rectifying HERG (*KCNH2*) cardiac potassium channel affecting the repolarizing I_{Kr} potassium current. This SQTS is a mirror image of the LQT2 variant.

Belloccq et al.⁵⁹ demonstrated that this disorder is genetically heterogeneous and can also be caused by a mutation in the *KCNQ1* gene. Analysis of candidate genes identified a g919c substitution in *KCNQ1* encoding the potassium channel affecting the repolarizing I_{Ks} potassium current. This SQTS genetic variant is the mirror image of the LQT1 variant.

Outward K^+ rectifier currents can both prolong and shorten the refractory period according to the heart rate. They may also mediate physiologic reactions. Certain antiarrhythmic drugs, specifically the methanesulfonanilide class of antiarrhythmic agents (E4031, dofetilide) blocks the rapid component (dofetilide-sensitive component). Macrolide antibiotics, such as erythromycin, spiramycin, azithromycin, roxithromycin, and clarithromycin; fluoroquinolone antibiotics such as levofloxacin, moxifloxacin, and ciprofloxacin; antifungal drugs such as ketoconazole and antihistamines such as

Figure 1. Electrocardiographic recordings in a 27-year-old male with short QT pattern. (A) 12-lead ECG showing a right bundle branch block pattern, prominent T waves, and QT and QTc intervals of 302 ms and 315 ms, respectively, at a heart rate of 67 beats/min. (B) 3-lead Holter ECG showing a transient episode of atrial fibrillation complicating the short QT interval syndrome.

terfenadine; all inhibit I_{KR} , and have been implicated in the acquired forms of LQTS. Based on pharmacology and distinct time and voltage-dependent properties two distinct components of potassium rectifier current were distinguished: the drug-insensitive component or I_{KS} , and the delayed rectifier component that activates one to two orders of magnitude faster, designed as ultra rapid-delayed rectifier potassium current or I_{KUR} .

The mutations dramatically increase I_{KR} or I_{KS} leading to heterogeneous abbreviation of action potential duration and refractoriness, and reduce the affinity of the channels to I_{KR} or I_{KS} blockers.

Atrial fibrillation has been mapped to chromosome 10, with dominant autosomal inheritance by mutation in the chromosome 10, in the q22-q24 region.^{60,61} One of the mapped genes, the 10q22 in the DLG5 region, is a member of the family of proteins of the so-called MAGUKs (membrane-associated guanylate kinase). This family of molecules medi-

ates intracellular signaling with diverse functions in the formation of cellular junctions, in maintaining the cellular morphology, and clustering of protein channels in the cellular surface. Only one portion of cDNA was assessed in the DLG5 region.

A family with persistent and hereditary atrial fibrillation had a mutation (S140G) detected and identified in the KCNQ1 gene (KvLQT1) of the 11p15.5 chromosome. The KCNQ1 gene encodes the pore that makes the alpha subunit of the I_{KS} channel. One functional analysis of the S140G mutation revealed a functional gain in the KCNQ1/KCNE1 and KCNQ1/KCNE channels. This fact contrasts with the negative effect or loss of function observed in the KCNQ1 channel in LQTS. Thus, the S140G mutation initiates and maintains the atrial fibrillation to reduce the duration of the refractory period of the monophasic action potential of atrial myocytes.⁶² Atrial fibrillation in the setting of a short QT interval may be correlated, and the usual

Table 2. Short QT Syndromes

A. Acquired and drug-related short QT syndrome	
Acidosis	
Alterations of the autonomic tone	
Digoxin toxicity and digoxin effect	
Hypercalcemia	
Hyperthermia	
Increased potassium plasma levels	
B. Hereditary short QT syndrome	
Linked to mutations in I_{KR} channel HERG (KCNH2): The mutations increase I_{KR} , leading to heterogenous abbreviation of the transmembrane action potential and refractoriness, and reduce the affinity of this channel to I_{KR} blockers. ⁴⁸	
Linked to mutation in I_{KS} channel in the KCNQ1 gene. ⁵⁹	

correction of QT interval for heart rate is inappropriate due to lack of QT interval dependency. Patients with short QT interval have a short atrial effective refractory period and a high incidence of atrial fibrillation suggesting similar disease process in atria and ventricles. Due to an increased risk of SCD, SQTs should be ruled out as a possible etiology in lone atrial fibrillation.

Brugada syndrome and congenital LQTS variant type 3 (LQT3) can share the same locus. In some patients, both disorders could be different aspects of

the same disease. The cardiac sodium channel gene, SCN5A, is involved in two such arrhythmogenic diseases. It is believed that these syndromes result from different molecular effects: Brugada syndrome mutations cause reduced sodium current, while LQT3 mutations are associated with a gain of function. Evidence shows that phenotypic overlap may exist between the Brugada syndrome and LQT3. One large family with a SCN5A mutation, and a "mixed" electrocardiographic pattern (prolonged QT interval and ST-segment elevation) has been reported. Moreover, the presence of "intermediate" phenotypes highlights a remarkable heterogeneity, suggesting that clinical features may depend upon the single mutation.³⁶ Greater understanding of the genotype-phenotype correlation will allow the definition of the individual patient's risk, and the development of guidelines for clinical management.

By analogy, we suggest the possibility of a link between congenital SQTs and LQTS of the LQT1/LQT2 types. LQT1 and LQT2 LQTS mutations cause a reduced outward K^+ rectifier current with prolongation of the action potential, while congenital SQTs is associated with an abbreviation of action potential duration and refractoriness. Table 3⁶³⁻⁶⁸ shows some of the differential characteristics of these disorders and possible therapies.

Table 3. Comparison and Contrast of Short and Long (Type 1 and 2) QT Syndromes

	SQTs	LQT1 and LQT2
Channel affected	I_{KR} delayed rectifier current I_{KS} delayed rectifier current	I_{KR} delayed rectifier current I_{KS} delayed rectifier current
Effect of mutation on channel	A gain of function	Reduced outward K^+ rectifier current Reduced outward K^+ rectifier current
Phase of action potential affected	Phase 3	Phase 3
Rhythm	High incidence of AF	Sinus
Heart rate	Normal when sinus	Frequent low heart rate for age
QRS axis	Frequently left-axis deviation	Normal
T waves	Tall peaked, pointed, narrow, and symmetrical	LQT1: broad-based prolonged T waves LQT2: low-amplitude with a notched, biphasic, or bifid T appearance
QT and QTc interval	Constant and uniform very short QT and QTc interval; ≤ 280 ms and ≤ 300 ms, respectively. Without significant dynamic changes during heart rate variations or on exertion	QTc > 0.47 , affected; QTc = $0.43-0.47$, considered border line; QTc < 0.43 , not affected
U wave	Normal	Prominent U waves may be present V_4-V_6
Therapy	ICD. Quinidine in association with ICD or quinidine alone in very young children or in developing and poor countries	ICD when syncope recurs, despite beta-blockage; left cardiac sympathetic denervation may be indicated in some patients

During programmed electrical stimulation (PES), short atrial and ventricular refractory periods and increased ventricular vulnerability to fibrillation were documented in SQTs. Clinicians need to be aware of this short QT pattern on the ECG, as it is a sign of high risk for SCD in otherwise healthy individuals.

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