Congenital Long QT-Syndrome

9

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9.1 Introduction

The *congenital long QT syndrome* (LQTS) is considered to be one of the hereditary cardiac arrhythmia syndromes, nowadays also known as cardiac *channelopathies*. The syndrome is characterized by prolongation of the heart rate *corrected QT-interval* (QTc) on the 12-lead electrocardiogram (ECG). In affected family members, it is associated with recurrent syncope, seizures, and *sudden cardiac death* due to *ventricular arrhythmias* (*Torsade des Pointes (TdP)* and *ventricular fibrillation*), which typically follow a precipitating event such as exertion, extreme emotion, swimming and diving, or auditory stimulation.

The congenital LQTS was first described in 1957 by Jervell and Lange-Nielsen in a family consisting of four children with a prolonged QT-interval on the electrocardiogram, congenital sensorineural hearing loss, recurrent syncope, and sudden cardiac death.[1] The inheritance pattern appeared to be autosomal recessive. A few years later, in the early 1960s *Romano*[2] and *Ward*[3] described independently of each other, families in which affected members had recurrent syncope, sudden cardiac death and QT prolongation on the electrocardiogram, however, without the associated deafness, and with an autosomal dominant mode of inheritance.

Breakthroughs in molecular genetics in the mid-1990s revealed the fundamental molecular basis of the LQTS, which in general relates to a defect in specific cardiac ion channels, caused by specific gene mutations.[4, 5] These defects result in either a decrease in repolarizing potassium currents or an inappropriate late entry of sodium in the myocyte eventually resulting in a prolonged QT-interval on the electrocardiogram.[6]

The diagnosis of LQTS is made by a careful evaluation of the personal and family history of the patient and a detailed examination of the electrocardiogram in order to detect either prolongation of the QT-interval or specific changes in the morphology of the ST-T segment. In addition to the 12-lead electrocardiogram, exercise testing and Holter monitoring may be useful.

In the majority of patients, the diagnosis can be confirmed by molecular genetic testing, which will reveal mutations in specific genes, mostly encoding for cardiac K^+ or Na^+ channels. Once the diagnosis has been made and therapy has been started, it is essential to identify the patient at risk for malignant ventricular arrhythmias because in that case a prophylactic ICD might be pertinent. In addition, screening of the first degree family members should be initiated, preferably in close collaboration with a clinical geneticist, in order to detect the asymptomatic or at the moment not yet diagnosed patient at risk.

This chapter will review the normal electrophysiological mechanisms involved in the cardiac action potential as well as the structure and function of the cardiac ion channels. Subsequently, a description of the congenital LQTS will be given.

9.2 Electrophysiological and Molecular Mechanisms

9.2.1 Cardiac Action Potential

The cardiac action potential (AP) reflects the integrated electrical activity of many ionic currents across the cell

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membrane through voltage-gated ion channels, ionic pumps, and ionic exchangers (Fig. 9.1). Depolarizing currents convey positively charged ions (Na^+, Ca^{++}) into the cell, while the repolarizing K^+ current flows to the outside of the cell (extensively reviewed in, e.g., Tan et al.[7] and Grunnet et al.[8])

The AP can be divided into five phases:

- Phase 4: the resting membrane potential is maintained by a balance between Na^+ and Ca^{++} leak currents and the inward rectifier current (I_{K1}).
- Phase 0: The cardiomyocyte membrane is depolarized by a rapid, transient influx of Na^+ ions through voltage-gated sodium channels (I_{Na}). This is reflected as the upstroke of the AP.
- Phase 1: during early repolarization, the transient efflux of K^+ through transient outward channels (I_{to}), which inactivate rapidly, terminates the AP upstroke.
- Phase 2: the plateau phase of the AP is maintained by a balance between an inward Ca^{++} current through L-type Ca^{++} channels and a K^+ efflux (I_{Kr} and I_{Ks}).
- Phase 3: during late repolarization the Ca^{++} channels have inactivated. The outward K^+ currents continue mainly through the slowly activating delayed rectifier K^+ channel (I_{Ks}). At the end a large outward K^+ current (I_{K1}) brings the membrane potential to its resting level.

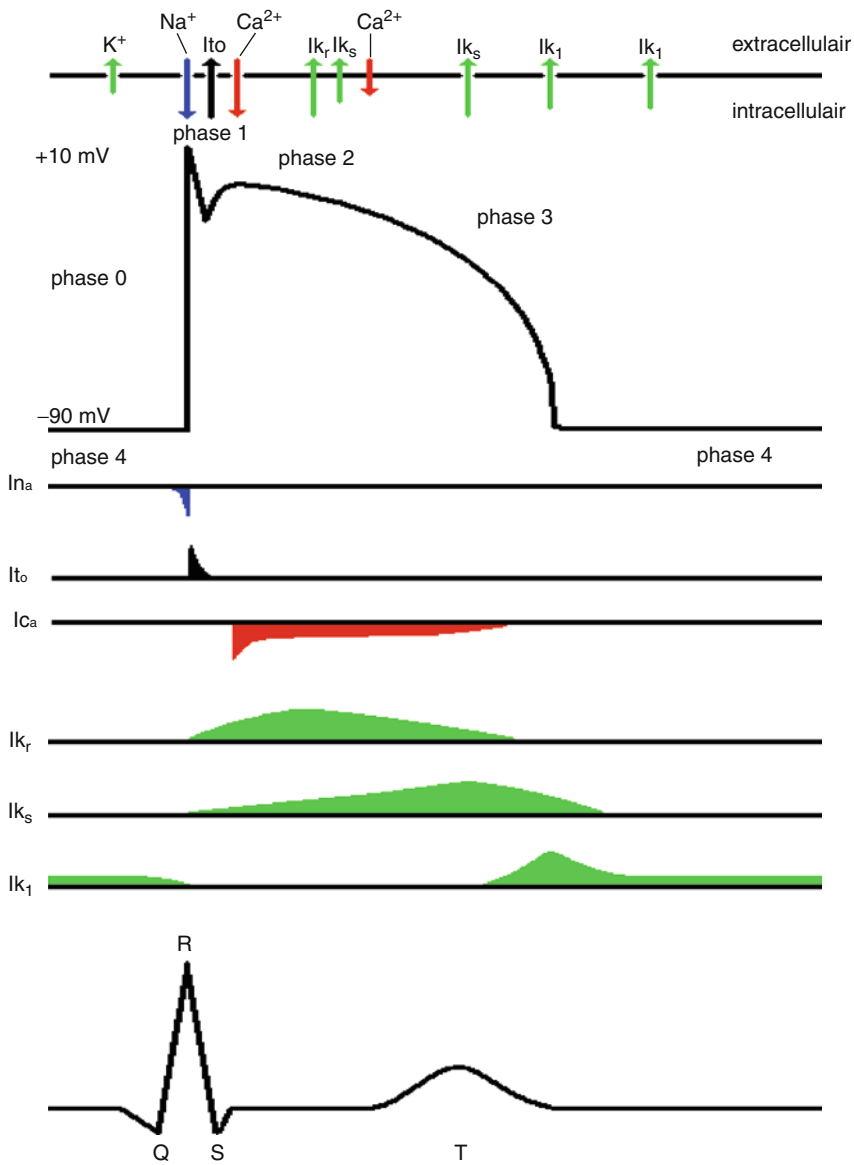

Fig. 9.1 Cardiac action potential (see text for explanation)

On the surface ECG, the QRS complex reflects the depolarization, and the T-wave reflects the repolarization phase of the ventricle. The T-wave is much longer than the QRS complex simply because repolarization takes longer than cardiac excitation.

The repolarization phase is not homogeneous in the ventricle, because of the fact that the ventricular wall consists of three different layers (epicardium, midmyocardium (M cell layer) and endocardium) with different action potential duration and configuration.[9,10] Voltage gradients between these layers during repolarization determine the height and the shape of the T-wave.

9.2.2 Cardiac Ion Channels

The structure of the voltage-gated potassium channel involved in most cases of LQTS includes a monomer of six membrane-spanning regions (S1–S6) with connecting intracellular cytoplasmatic loops, a voltage-sensing domain (S4), and a pore region located between S5 and S6 (Fig. 9.2). A tetrameric structure of four individual monomers together will eventually form a functional hydrophobic envelope, which surrounds a central cavity or pore. These four pore forming α-subunits are known to be modulated in their biophysical properties, pharmacologic responses, tissue distribution, and intracellular trafficking by smaller accessory β-subunits. These β-subunits often have a single membrane-spanning domain (Fig. 29.2).

The structure of the cardiac sodium (SCN5A) and L-type calcium (CACNA1C) channels is more complex. They consist of a single protein with four homologous domains (the alpha-subunits), each of which contain six transmembrane domains, similar to the four linked potassium channel modules (for figure see chapter on Brugada syndrome).

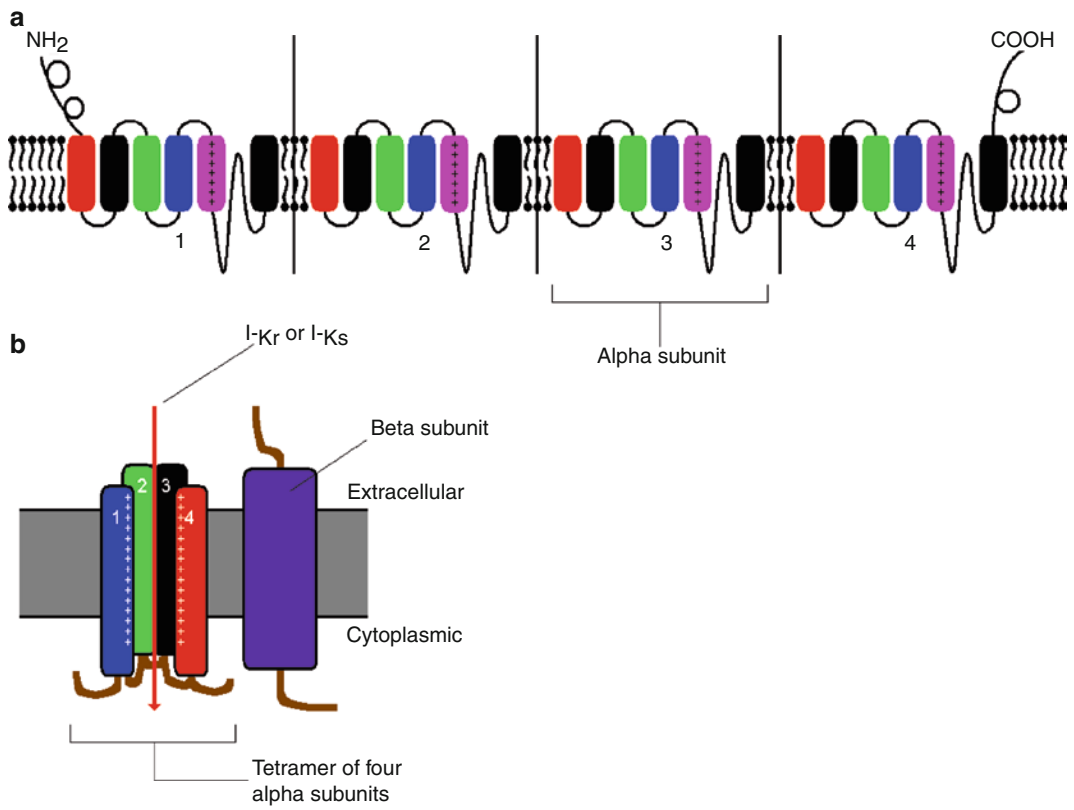

Fig. 9.2 (**a**) Schematic topology of the four α-subunits (K_vLQT1 or hERG) of a voltage-gated potassium channel. Characteristic are the six membrane-spanning segments of the α-subunit. Four of those α-subunits (number 1–4) form a tetrameric potassium channel, which is responsible for the I_{Ks} or I_{Kr}. This is showed in (**b**), which includes the β-subunit (respectively MinK or MiRP1) that can modulate the function of the α-subunits

9.3 Epidemiology and Prevalence

The prevalence of congenital LQTS in the USA has been estimated to be approximately 1 in 5,000 individuals, causing hundreds to thousands of sudden cardiac deaths in children, adolescents, and young adults each year.[11] However, the prevalence of congenital LQTS may be as high as 1 in 2,000–3,000 live births. This figure is derived from the largest prospective study of neonatal electrocardiography ever performed in 44,596 infants at age 3–4 weeks.[12] The investigators concluded that the prevalence in their population must be close to 1:2,500 at least. Since most mutation carriers remain asymptomatic throughout life, clinical disease is less common. Nevertheless, LQTS is one of the most common causes of autopsy-negative sudden unexplained death.[13]

The congenital long QT syndrome can be divided in two distinguishable forms: the Romano-Ward syndrome (RWS) and the Jervell and Lange-Nielsen syndrome (JLNS). The RWS is the most common form of the LQTS and accounts for over 99% of cases. It is transmitted as an autosomal dominant trait and it can be divided into 12 subtypes (LQT1 to LQT12). The extremely rare, autosomal recessive, JLNS is associated with congenital deafness.

9.4 Molecular Genetics and Pathogenesis

9.4.1 Molecular Genetics

Advantages of molecular genetics in the last decade of the twentieth century have provided insights into the mechanisms underlying the LQTS. The genetic defects causing the LQTS are for the majority of cases located in genes encoding for the α- and β-subunits of the voltage-gated potassium channels (e.g., KCNQ1, KCNH2, KCNE1 and KCNE2). On the other hand, mutations in the genes encoding for the cardiac sodium (SCN5A) and calcium channel (CACNA1C) can also result in prolongation of the QT-interval. Finally, genes encoding for several structural membrane scaffolding proteins or proteins interacting with these cardiac channels are responsible for some exceptional types of LQTS. Since the first description of LQTS, over 300 mutations have been described in 12 distinct LQTS-related genes[14–17](Table 9.1).

The dysfunction of the ion channels is caused by two distinct biophysical mechanisms, consisting of coassembly or trafficking defects and of the formation of channels with aberrant function.[15] In the case of coassembly

Table 9.1 LQTS subtypes and corresponding determinants

	Chromosome	Gene	Protein	Function	Current
LQT 1	11p15.5	KCNQ1	KvLQT1	α-Subunit	I_{Ks}
LQT 2	7q35-36	KCNH2	hERG	α-Subunit	I_{Kr}
LQT 3	3p21-24	SCN5A	Nav1.5	α-Subunit	I_{Na}
LQT 4	4q25-27	Ankyrin-B	Ankyrin-B	Scaffolding	I_{Na}
LQT 5	21q22	KCNE1	MinK	β-Subunit	I_{Ks}
LQT 6	21q22	KCNE2	MiRP1	β-Subunit	I_{Kr}
LQT 7	17q23	KCNJ2	Kir2.1	α-Subunit	I_{K1}
LQT 8	1q42	CACNA1C	Ca(v)1.2	α-Subunit	I_{Ca}
LQT 9	3p25	CAV3	Caveoline-3	Scaffolding	I_{Na}
LQT 10	11q23.3	SCN4B	Nav1.5	β4-Subunit	I_{Na}
LQT 11	7q21-22	AKAP9	Yotiao	ChIP	I_{Ks}
LQT 12	20q11.2	SNTA1	α1-syntrophin	ChIP	I_{Na}

ChIP channel interacting protein; *Scaffolding* structural membrane scaffolding proteins

defects, the mutant subunits are not transported properly to the cell membrane and fail to incorporate into the tetrameric channel. The net effect will be a 50% or less reduction in channel function (haploinsufficiency). The second biophysical mechanism consist of the formation of defective channels in which the product of the mutated gene, being an abnormal protein, is transported to the cell membrane and incorporated in the channel subunit. This will lead to a dysfunctional channel, resulting in a more than 50% reduction in channel current (dominant-negative effect).

The LQTS type 1 (50% of cases) and type 2 (35–40% of cases) are caused by pathogenic mutations in genes encoding the α-subunits of two specific voltage-gated potassium channels resulting in impairment of the delayed rectifier current. The delayed rectifier current comprises of two independent components: one slowly activating (I_{Ks}, KCNQ1, LQT1) and one rapidly activating (I_{Kr}, KCNH2, LQT2) component. The pathogenic mutations will lead to a "loss of function" of the relevant ion channel and as a consequence of that to a reduction of repolarizing potassium current.[18] This reduction in the repolarizing potassium current results in a prolongation of the action potential duration and thereby to the creation of the arrhythmogenic substrate.

"Gain of function" mutations in the SCN5A-encoded sodium channel protein, which are associated with prolonged depolarization due to a small persistent inward current (I_{Na}), are the cause of the LQTS type 3 (LQT3, 10–15%).

Rare subtypes of the LQTS stem from mutations in genes encoding for the β-subunits of several cardiac ion channels, which causes a disturbance of their function. They include KCNE1 encoding the β-subunit of the voltage-gated potassium channel responsible of the slowly activating potassium current I_{Ks} (minK, LQT5, 2–3%), KCNE2 encoding the β-subunit of the voltage-gated potassium channel responsible for the rapidly activating potassium current I_{Kr} (MiRP1, LQT6, <1%) and the SCN4B-gene encoding the β4-subunit of the I_{Na} sodium channel (LQT10, <1%).

The LQT1, LQT2, LQT3, LQT5, LQT6, and LQT10 make up the classic forms of the congenital LQTS and it is this group of ion channel genes that has characterized this primary electrical heart disease as a pure cardiac channelopathy.

During the past years, mutations in other genes have been identified resulting in QT prolongation in single individuals or just a few families. These LQTS-related disorders involve mutations in the ankyrin-B gene (LQT4), which product function as a cytoskeletal membrane adapter as ankyrin-B is involved in anchoring of ion channels to the cellular membrane and mutations in the caveolin-3 gene with increase in late sodium current (LQT9).[19, 20] Other rare LQTS-variants are syndromes associated with abnormal cardiac repolarization. One of these syndromes is the Andersen–Tawil syndrome (LQT7 or ATS1), due to mutations in the KCNJ2-encoded Kir2.1 potassium channel (reduced I_{K1} current), with a phenotype dominated by minor skeletal (facial) abnormalities and periodic hypokalemic paralysis.[21,22] Another syndrome is the Timothy syndrome (LQT8 or TS1), which is caused by mutations in the a-subunit of the L-type calcium channel, which leads to an increase in Ca(v) 1.2 current. The Timothy syndrome involves, among others, a typical syndactyly in hands and feet, mental retardation/autism, and many more features.[23]

The autosomal recessive variant of the LQTS (JLN syndrome) arises in patients who inherit abnormal KCNQ1 or KCNE1 alleles from both parents, who are usually without symptoms themselves. The abnormal alleles can bear the same mutation as is usually the case in consanguineous families or be different (compound heterozygosity).[24]

In this chapter, we will focus on the clinically most relevant forms of the LQTS, which are the LQT1, LQT2, and LQT3 subtypes.

9.4.2 Mechanisms Involved in Arrhythmia

Torsade de Pointes is the classical ventricular arrhythmia associated with LQTS. These TdP are either pause dependent (LQT2) or may be induced during higher heart rates without a preceding pause (LQT1).[25] Pause-dependent TdP, common in LQT2, is triggered by early afterdepolarizations (EAD), caused by Ca^{2+} release from intracellular Ca^{2+} stores.[26] Subsequently, Ca^{2+}-dependent transmembrane currents are altered in such a way as to allow L-type Ca^{+} channels to recover more readily from inactivation and to reactivate before repolarization is complete, thus generating EADs. On the other hand, in LQT1 the induction of TdP is not pause dependent, suggesting a role for delayed afterdepolarizations (DAD), secondary to intracellular Ca^{2+} overload.[27] Experimental studies have shown that blockade of the I_{Ks} causes DAD.[28]

Prolonged repolarization may result in reentry through dispersion of repolarization. Augmented spatial dispersion of repolarization within the ventricular myocardium can lead to a unidirectional block in conduction and set the stage for reentry, which is the principal arrhythmogenic substrate.[29,30] The reentry mechanism is initiated by an extraventricular beat (EAD or DAD).

Especially, in the LQT1 patients, events will occur during higher heart rates. Stimulation of the β-adrenergic receptor by epinephrine will lead to an increased activity of the intracellular adenylyl cyclase activity, which increases cAMP.[31] cAMP will activate protein kinase A, which phosphorylates among others, the K^+ channels. Phosphorylation of K^+ channels will enhance I_{Ks}, resulting in a reduction of the action potential duration.[32] The shorter duration of the action potential is reflected in a shorter QT-interval during an increase in heart rate.[33] In the case of LQT1 and LQT5, the I_{Ks} channels are not able to adjust to an increase in heart rate, which will lead to an abnormal response to adrenergic stimulation with impaired shortening of the action potential and subsequent progressively prolonged QTc during exercise and early recovery. Beta-adrenergic regulation of I_{Kr} (LQT2) is more complex (reviewed[34]). Differential results were found in studies indicating either a reduction or an increase of I_{Kr} in response to β-adrenergic stimulation. The exact mechanisms of action are beyond the scope of this chapter.

The rationale for treatment with β-blockers in patients with LQTS (especially LQT1 and LQT2) is the prevention of calcium overload in both types of LQTS by preventing the loading of intracellular Ca^{2+} stores by cyclic adenosine monophosphate level (cAMP)-dependent processes, notably Ca^{2+} influx through L-type Ca^+ channels.[35] Furthermore, direct effect on the β-adrenergic modulation of I_{Ks} and I_{Kr} currents are responsible for the therapeutic effect. The exact mechanisms are again beyond the scope of this chapter.

The "gain of function" mutations in the sodium channel in the case of LQT3 results in a persisting depolarizing inward sodium current during the plateau phase of the action potential and as a consequence of that to a prolongation of the repolarization as well. The increase in the I_{Na} is especially important during slow heart rates. During fast heart rates, the effect of the pathogenic mutation is less because Na^+ will accumulate in the cell. This phenomenon will lower the Na^+ gradient across the membrane and thereby the magnitude of I_{Na}[36], *r*esulting in a shorter QT-interval during exercise, even more than normal.[37]

9.5 Clinical Aspects

9.5.1 Clinical Presentation in General

The clinical picture of the LQTS is diverse. It can vary from a lifelong asymptomatic course in approximately half of the patients with genetically proven LQTS to recurrent syncopal attacks, seizure like episodes, and premature sudden cardiac death in others. The considerable variation in the phenotype of LQTS (incomplete penetrance) is presumably caused by several modifying factors, including genetic polymorphism at the mutated locus and environmental factors. Underlying the presenting symptoms, syncope, ACA and SCD are polymorphic ventricular tachyarrhythmias in the form of TdP, and ventricular fibrillation. These TdP are most often self-limiting but in some cases they degenerate into ventricular fibrillation leading to sudden death. Syncope is the most frequent symptom in LQTS. Among symptomatic probands, approximately 50% will experience their first cardiac event (syncope or death) before the age of 12 and by the age of 40 this is increased to approximately 90%.[38] Less than 5% of the LQTS patients will present with sudden cardiac death (SCD) or aborted cardiac arrest (ACA) as first symptom. Conversely, however, less than half of the sudden death victims with LQTS experienced a prior warning episode of syncope, which means that the occurrence of ventricular fibrillation is unpredictable in many cases. In the majority of LQTS patients, cardiac events will be triggered by physical activity, emotional stress, or rest.

9.5.2 Genotype–Phenotype Specific Correlations

The clinical course of LQTS is in particular dependent on the genotype concerned (Table 9.2). By the age of 15, more than 60% of LQT1 patients have had a cardiac

Table 9.2 Clinical characteristics in the common forms of LQTS

	LQT1	LQT2	LQT3
Prevalence (%)[45]	50	35–40	10–15
Events occurring with exercise or emotion (%)[40]	88	56	32
Events occurring at rest or sleep (%)[40]	3	29	39
Lethal events occurring with exercise or emotion (%)[40]	82	29	16
Lethal events occurring at rest or sleep (%)[40]	9	49	64
Specific triggers	Swimming/diving	Loud noise	Sleep/rest
Pause dependency in TdP onset[25]	–	++	+/-?
Augmented risk postpartum[94]	+	+++	+
Median age first event[39]	9	12	16
Events < 10 year (%)[39]	40	16	2
Events < 40 year (%)[39]	63	46	18
Death during event (%)[39]	4	4	20
Sudden death as presenting symptom (%)[39]	2	1	3
Efficacy of β-blocker	+++	++	+?

TdP torsades de pointes

event, compared to less than 10% in LQT3 patients.[39] The number of events that occurred till the age of 40 was also higher in LQT1 (63%) or LQT2 (46%) than LQT3 (18%). In contrast, the likelihood of death per cardiac event is much higher in LQT3 (20%) than in LQT1 and LQT2 (4%).[39]

The triggers for arrhythmic episodes and cardiac events also depend on the genotype.

LQT1 patients experience the majority of their events during intensive physical exercise, emotional stress, or other conditions associated with elevated sympathetic activity such as anger and fright.[40] Very specific and particularly frequently occurring triggers for malignant ventricular arrhythmias in LQT1 patients are swimming and diving.[41,42] The symptoms in LQT2 patients occur both during exercise and in rest. In fact, 15% of events occurred in rest and/or sleep. Auditory stimuli such as telephone ringing, doorbell ringing, or the sound of an alarm clock are very specific triggers for LQT2-related life-threatening arrhythmias.[43] Patients with LQT3 are at particularly high risk for cardiac events at rest or during sleep, because their QT-interval is excessively prolonged at slow heart rates.[40]

9.5.3 Clinical Diagnosis

The clinical diagnosis of LQTS is made by a solid evaluation of the history of the patient. In addition, a careful inquiry about family history of unexplained sudden death or recurrent syncope at young age is of great importance. Take notice of unexpected drowning in a good swimmer, road traffic accidents without obvious cause, familial epilepsy, and sudden infant death, which are all suspicions for possible malignant ventricular arrhythmias. Finally, sudden death with negative postmortem examination should trigger a family investigation for several cardio-genetic diseases including LQTS.

In addition to clinical history, it is important to conduct a precise examination of the electrocardiogram (ECG) at rest and/or during exercise (Table 9.3).

Table 9.3 Electrocardiographic characteristics in LQTS type 1-3

	LQT 1	LQT 2	LQT 3
Normal QTc (<440 ms) male (%)[109]	56	33	29
Normal QTc (<460 ms) female (%)[109]	64	55	61
QTc shortening with exercise	<Normal	Normal	>Normal
Specific ST-T wave abnormalities	Broad-based and prolonged T waves	Widened, bifid T; low amplitude T in lead II, III, and avF	Long isoelectric segment with late appearing T with sharp deflection
Signs of sinus node dysfunction at rest[38,63]	+	–	++
Signs of sinus node dysfunction during exercise[38,63]	+	–	–
QT prolongation in response to epinephrine (steady state)[67]	+	–	–

Screening ECGs from family members may be informative as well. Structural heart diseases should be excluded by echocardiography or MRI-scanning.

9.5.4 Clinical Diagnostic Criteria

The typical cases of LQTS patients present no diagnostic difficulty for most of the physicians aware of the disease. In other cases it can be troublesome and more variables are necessary than clinical history and ECG only. To overcome these problems, diagnostic criteria were first proposed in 1985 by Schwartz and colleagues.[44] The latest diagnostic criteria are listed in Table 9.4.[45] The score ranges from 0 to 9 points and contains three diagnostic probabilities: low probability (0–1 point), intermediate probability (2–3 points), and high probability of LQTS (3½ points or more).

One should consider that these criteria have been defined in the pre-molecular era and should be used with common sense. They should be used only for the diagnosis of LQTS for a patient who is suspected to have the disease on clinical ground.

9.5.5 QT-Interval

The QT-interval on the ECG is defined as the time interval between the onset of QRS complex and the end of the T-wave. The end of the T-wave is defined as the intersection of a tangent[46] to the steepest slope of the last limb of the T-wave and the baseline, in lead II or V5 and V6. This value has to be corrected for the heart rate according to the Bazett's formula by dividing it by the square root of the preceding RR interval in seconds. (QTc = QT-interval/square root of RR interval).[47] However, at slow heart rates there is an overcorrection and at fast heart rates there is an undercorrection of the QTc. Calculations should be based on the longest QT-interval measured. When sinus arrhythmia exists, an average QTc of at least three consecutive QRST complexes in lead II has to be calculated.[48] It is of great importance that the QTc is calculated manually by a physician with expertise in LQTS because it can be quite difficult in some cases.[49,50]

Before the beginning of the molecular era in LQTS, QTc in excess of 440 ms in males and 460 ms in females were considered prolonged.[51,52] The longer QTc in women become evident after puberty, suggesting a role for hormonal changes. Nowadays we know that there is a considerable overlap in QTc between "normals" and LQTS patients. Healthy individuals can have QTc up to 480 ms and many genetically proven LQTS patients have QTc within normal limits (<440–460 ms). This means that a normal QTc does not rule out a genetic predisposition to LQTS,[53] a consequence of the reduced penetrance of the LQTS. In fact, 10–50% (depending on genotype) of genetically proven LQTS patients do not show overt QT prolongation on a baseline ECG.[11,54,55] However, data

Table 9.4 1993–2006 Long QT syndrome (LQTS) diagnostic criteria (From Crotti et al. [45])

			Points
Electrocardiographic findings [a]			
A	QTc[b]	> 480 ms	3
		460 – 470 ms	2
		450 – 459 (male) ms	1
B	Torsade de pointes [c]		2
C	T wave alternans		1
D	Notched T wave in 3 leads		1
E	Low heart rate for age [d]		0.5
Clinical history			
A	Syncope [c]	with stress	2
		without stress	1
B	Congenital deafness		0.5
Family history [e]			
A	Family members with definite lqts		1
B	Unexplained sudden cardiac death below age 30 among immediate family members		0.5

[a]In the absence of medications or disorders known to affect these electrocardiographic features
[b]QTc calculated by Bazett's formula where QTc = QT/√RR
[c]Mutually exclusive
[d]Resting heart rate below the 2nd percentile for age
[e]The same family member cannot be counted in A and B
Score:≤1 point = low probability of LQTS
>1 to 3 points = intermediate probability of LQTS
≥3.5 points = high probability of LQTS

from the Mayo LQTS clinic show that a QTc value < 400 ms has a virtually 100% negative predictive value and that a QTc of 480 ms or more almost always indicates acquired or congenital LQTS. For screening purposes, in the general population, we advise to consider QTc of 470 ms or more as prolonged to maximize both the positive and negative predictive values.[12] In general practice, one can use the three-level ECG classification, which is described by Goldenberg et al.[56] (Table 9.5).

9.5.6 T Wave Morphology

LQTS patients often have an abnormal, genotype specific morphology of the ST-T segments, independently of the duration of the QT-interval (Fig. 9.3a–c). These T-wave abnormalities may be evident particularly in the lateral precordial leads. LQT1 patients typically have broad-based and prolonged T waves.[57] In contrast, LQT2 patients typically have characteristic widened bifid T-waves, mostly low in amplitude in the extremity leads.[58] A notch above the apex of the T-wave (G2 notch) often indicate LQT2, but is not commonly found

Table 9.5 Practical three-level ECG classification (Adapted from Goldenberg et al.[56])

Rating	1–15 years	Adult male	Adult female
Normal	<440 ms	<430 ms	<450 ms
Borderline	440–460	430–450	450–470
Prolonged	>460 ms	>450 ms	>470 ms

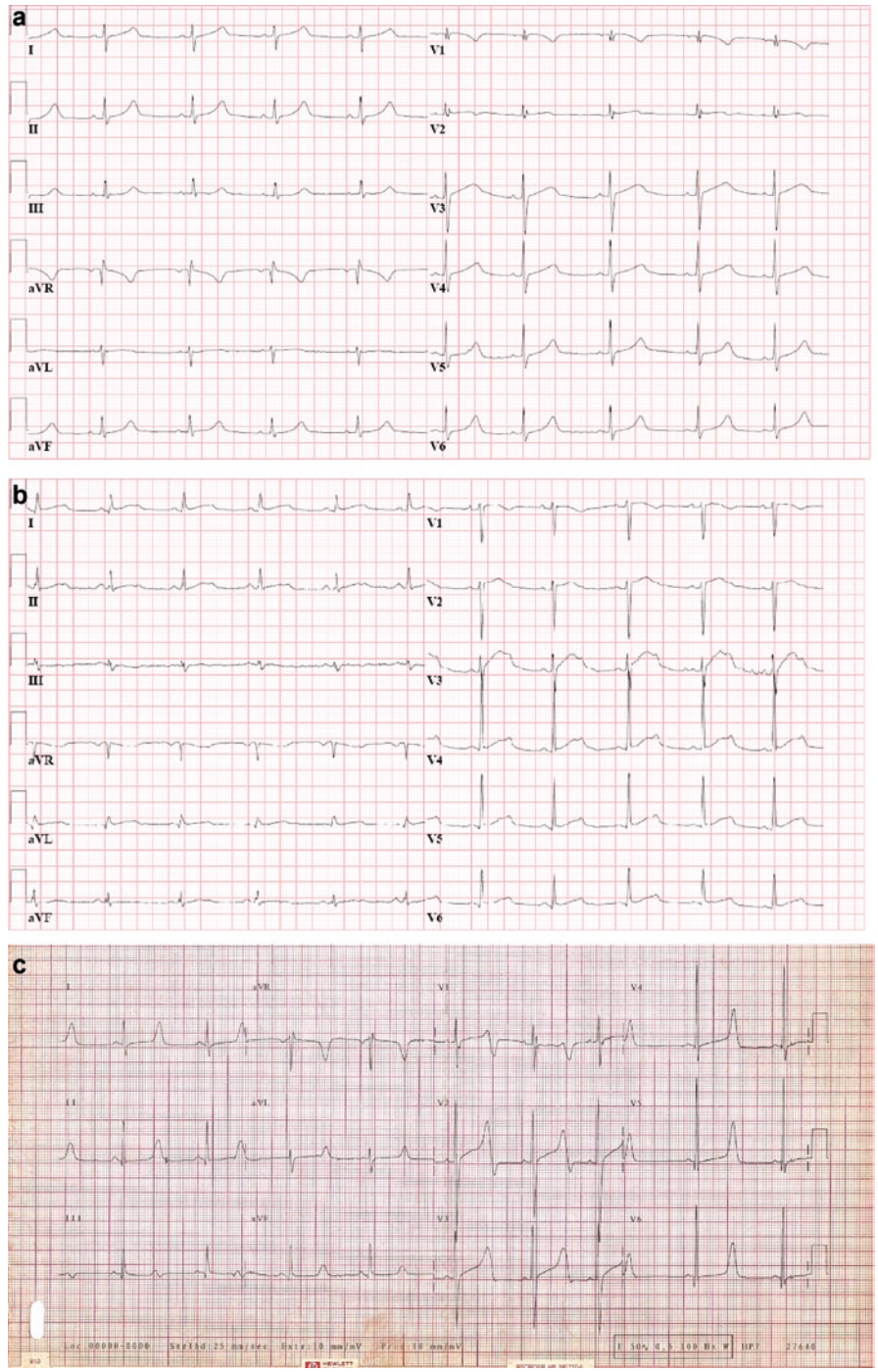

Fig. 9.3 (**a**) LQT1; (**b**) LQT2; (**c**) LQT3

on the baseline ECG.[59] They can appear, however, under low-dose epinephrine testing and so unmask a concealed LQT2.[60] Finally, LQT3 patients have a long isoelectric segment with a late-appearing T-wave with a relatively sharp deflection and a normal duration; however, this can also be seen in LQT1 patients.

9.5.7 T Wave Alternans

Beat-to-beat alternation in the T wave morphology, in polarity or amplitude, may be present in rest for brief moments but most commonly appears during emotional or physical stress and may precede TdP. It is a marker of major electrical instability and regional heterogeneity of repolarization and it identifies patients at high risk for malignant arrhythmias.[61]

9.5.8 QT-Dispersion

QT-dispersion is defined as the difference between the maximal and minimal QT-intervals in the 12 standard leads. It is increased in LQTS patients and it has been described as an arrhythmic marker; however, normal values are not available.[62]

9.5.9 Sinus Node Dysfunction

Signs of sinus node dysfunction, consisting of sinus bradycardia, sinus pauses, and a lower than expected heart rate during exercise have been reported in LQTS patients.[38] Slow heart rates can be particularly striking in younger children. In addition, LQT3 carriers regularly present with significant sinusbradycardia and sinus pauses at rest.[63]

9.5.10 Holter Monitoring

Holter monitoring during 24 or 48 h may aid in the evaluation of LQTS, but caution must be taken because normal values of maximal QTc are lacking at the moment. A holter-recorded maximum QTc greater than 500 ms does not equal LQTS! The value in holter monitoring lies in detecting T wave abnormalities suggestive of LQTS in patients with borderline QT prolongation and uncertain clinical diagnosis.[59] Sometimes 24-h ECG-monitoring can be useful in detecting bradycardia-induced QT prolongation in LQT3 patients or pause-dependent QT prolongation in LQT2 patients. In fact, in many cases of LQT2 patients, the onset of TdP is typically pause dependent, being initiated by a short-long-short sequence of preceding RR intervals.[25] This phenomenon is absent or rare in LQT1 patients. In addition, one can use holter monitoring for detection of ECG-signs of high electrical instability, for example, T wave alternans and QT-dispersion for risk stratification in known LQTS patients.

9.5.11 Exercise Testing

Exercise testing can be performed to identify a concealed LQTS patient (especially LQT1) or can be done in patients having already a diagnostic QTc at rest. LQT1 patients have an inadequate shortening of QTc with increasing heart rates and an exaggerated prolongation of the QT-interval after exercise.[64] In addition, they may have a diminished chronotropic response.[65] In LQT2 patients, the chronotropic response to exercise usually is normal as is the shortening of the QT-interval. In LQT3, the QT-interval shortening is slightly more than normal.[37] Exercise-induced ventricular ectopy is uncommon in LQTS and should prompt suspicion for catecholamine-induced polymorphic ventricular tachycardia.[66]

9.5.12 Epinephrine Stress Test

A substantial part of patients with LQTS have a normal QTc at baseline (10–50%), especially LQT1 patients. To unmask these concealed mutation carriers or low penetrant patients, a provocation test with epinephrine can be useful, again especially in LQT1.[67] The two proposed protocols that exists for epinephrine QT stress testing include the escalating-dose protocol by Ackerman's group ("the Mayo protocol")[67] and the bolus injection followed by brief continuous infusion by Shimizu's group ("the Shimizu protocol").[68]

Both protocols are safe and well tolerated. Induction of TdP or ventricular fibrillation is uncommon. However, their use in clinical practice is debated because normal subjects also showed QT- and QTc prolongation, in varying degree, in response to epinephrine infusion, and normal values are missing at the moment. The specificity of the proposed criteria for epinephrine provocation in diagnosis of the LQTS

is variable; however, paradoxical QT prolongation at low-dose epinephrine (Mayo protocol) or a QTc > 600 ms at any dose is highly specific.[69]

9.5.13 Differential Diagnosis

In typical cases of syncope and clear prolonged QT-interval on the ECG the diagnosis of congenital LQTS can be quite simple. In borderline cases, however, the following conditions should be considered: acquired long QT syndrome, vasovagale syncope, orthostatic hypotension, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, catecholamine-induced polymorphic ventricular tachycardia, and epilepsy. Most of these disease-entities can be demonstrated or ruled out with additional cardiological evaluation.

The acquired long QT syndrome can be secondary to or associated with drug-therapy, myocardial ischemia, several cardiomyopathies, heart failure, left ventricle hypertrophy, hypokalemia, hypocalcemia, hypomagnesemia, autonomic influences, hypothyroidism, and hypothermia.

Drugs that prolong the QT-interval include antiarrhythmic agents such as sotalol and amiodarone and many non-cardiovascular drugs such as haloperidol. Most drugs that cause TdP block the rapid component of the delayed rectifier current, and previously unrecognized LQTS, of any sub-type, can be identified in 5–20% of patients with drug-induced TdP.[70] In addition, several genetic alterations have been identified that predispose people to drug induced QT-interval prolongation.[70,71]

9.6 Molecular Genetic Diagnosis

Until recently the LQTS was a pure clinical diagnosis, but nowadays commercially available molecular screening is becoming more and more part of the routine diagnostic process. The genetic testing may also provide additional information, which can be used for the risk stratification process and the way of treatment. Detailed genetic counseling by a clinical geneticist and a cardiologist is warranted before testing, particularly for asymptomatic persons for whom the option of not testing must also be discussed.

Genetic testing for the common subtypes of LQTS can identify a mutation in 50–75% of probands in whom the diagnosis appears to be certain on clinical grounds.[72] It is important to notice that a negative genetic test in a subject with clinical LQTS does not rule out the diagnosis! The false negative ones are probably due to technical difficulties with genotyping, noncoding variants, or as yet unidentified disease-associated genes.

The specific clinical picture and/or the typical abnormalities on the ECG can guide the mutation analysis as they can suggest the affected gene in 70–90% of patients.[73,74]

The identification of the pathogenic mutation in the proband is also of great importance for family screening, because it allows for the identification of all affected family members potentially at risk for sudden cardiac death, even those who are asymptomatic and have a normal QTc. These concealed LQTS patients constitute a significant minority (25–50%) of the total LQTS population.[75] Identification of asymptomatic mutation carriers is important because preventive measures as avoidance of QT-interval prolonging drugs can be taken and screening of their children, who may have or develop more severe disease, is indicated as well.

Hundreds of mutations in the 12 genes linked to the LQTS have been identified thus far. Most reported mutations are in the coding regions of the gene, although noncoding mutations, which result in the loss of allele expression, have also been described (in the potassium channel genes). Also larger genomic rearrangements, for example, deleting a large part or the entire KCNQ1 gene, can occur. Most families have their own mutations, which are often termed "private" mutations. In most cases of LQTS, the mutation involved is a missense mutation (>70%). In other cases, it can be a frameshift mutation (10%), in-frame deletion, nonsense mutation, or splice-site mutation.[14]

One should be aware of the fact that genetic testing for LQTS-genes also has the potential for false positive results, since detection of a previously undescribed mutation with unknown significance does not establish the diagnosis. Further analyses by linkage within a family or in vitro studies may be necessary to establish the functional significance of the specific mutation found.

Molecular genetic testing may also be of help in avoiding misdiagnoses. This was demonstrated by the recent data from Taggart and colleagues, who showed that genetic testing of patients in combination with a superb clinical evaluation by a specialized cardiologist may

improve the diagnostic process because a large minority of individuals referred as having LQTS were found to be unaffected based on frequently occurring miscalculation of QTc or misinterpretation of symptoms.[76]

In addition, testing of non-LQTS-related genes can lead to the correct diagnosis in specific cases. Tester and colleagues found ryanodine receptor gene mutations responsible for the primary arrhythmia syndrome "catecholaminergic polymorphic ventricular tachycardia" in 17 of 269 (6.3%) patients with negative LQTS genetic testing.[77]

Genetic testing has not been evaluated so far in patients presenting with syncope, borderline QTc interval, and a negative family history. For them the incidence of false positive and false negative test results and their implications for therapy currently remain unknown.

9.7 Risk Stratification

The clinical course of LQTS is variable even within families because of incomplete penetrance. It is influenced by age, gender, genotype, environmental factors, therapy, and probably modifier genes. Continuous *risk assessment* for life-threatening cardiac arrhythmias is warranted in LQTS patients, because the risk for the individual patient may vary during life.

The main clinical risk factors consist of gender, QTc duration, and a history of syncope.

The genetic risk factors for malignant ventricular arrhythmias are mainly determined by the biophysical function of the mutations and the location of the mutation in the gene, rather than the specific type of LQTS.

9.7.1 Gender

Data from the international LQTS Registry demonstrate that the phenotype shows major time-dependent gender differences in the risk of cardiac events (syncope, ACA, SCD).[78] The rate of fatal or near-fatal events in children is significantly higher among boys than among girls throughout childhood, despite the fact that girls have longer QTc intervals. Male gender is independently associated with a significant increase in the risk of these events before age 15, whereas a gender risk reversal was shown to occur after age 14.[79] During childhood, LQT1 boys have significantly more risk of syncope, ACA or SCD, than LQT1 girls.[80] There was no difference between boys and girls with LQT2 and LQT3. More recent studies analyzed only risk factors for life-threatening cardiac events and did not investigate syncopal events.[81–83] These studies demonstrated that the cumulative risk for ACA and SCD in children (age 1–12) was 5% in boys and 1% in girls ($p < 0.001$).[83] After 16 years, females, both in LQT1 and 2, have a higher risk of cardiac events than males. They maintain higher risk than male patients throughout late adolescence and during adulthood.[81–83] In adulthood (age 40–60) the LQTS-related risk in women continues to be high, whereas event rates among affected men are not significantly different from those observed in unaffected men.[84] However, in affected men over age 40 the risk of ACA or death is similar to the risk in affected women. This means that the higher arrhythmic risk for LQTS women over 40 counterbalances the increased male risk due to acquired cardiovascular diseases. The mechanisms behind these age-specific gender differences are unknown. In theory, they are caused by environmental (epi), genetic, or hormonal factors.

9.7.2 QTc Duration

A baseline QTc of >500 ms in LQTS patients is associated with a high risk of syncope, ACA or SCD. Recent data showed that the baseline QTc in LQTS patients is also a major risk factor for life-threatening cardiac events (ACA or SCD) only.[81–83] In adolescents a QTc > 530 ms was associated with a significant increase in the risk of ACA or SCD compared with shorter values.[81] Adults with a QTc > 500 ms carry a significantly increased risk.[82] There appears to be considerable variability in the QTc interval when serial ECGs of one patient are recorded The maximum QTc interval measured at any time seems to be the strongest predictor.[85]

9.7.3 Time-Dependent Syncope

Recent data from the international LQTS Registry demonstrated that a history of syncope, assessed as a

time-dependent factor, is the most powerful predictor of life-threatening cardiac events.[81–83] The time of occurrence and frequency of the syncopal events affect outcome. In adolescents (age 10–20) the risk is increased 18-fold when there have been two or more syncopal events in the last 2 years. The risk is increased 12-fold when there was only one syncopal event during the last 2 years. Any syncope 2–10 years ago increased the risk by a factor 3.[81] In adults (age 18–40), time-dependent syncope after age 18 gives a > fivefold increase of the risk, while a syncopal event before age 18 was not a significant factor.[82]

9.7.4 Stratification of Risk

LQTS risk groups may, in general, be categorized as high, intermediate, and low.[86] The high risk group consists of patients with a history of aborted cardiac arrest and/or documented torsades des pointes. The intermediate risk group consists of subjects with time-dependent syncope and/or QTc > 500 ms. Patients in the low risk group did not experience any syncope and have a QTc < 500 ms.

9.8 Specific Risk Factors

9.8.1 Biophysical Function and Location of the Mutation

Recent genotype–phenotype studies from the international LQTS Registry have provided important information about the effect of location, coding type, and biophysical function of the channel mutations on the manifestation and clinical course of LQTS patients.[87,88] The biophysical function appeared to be an important determinant of outcome. In a study of 600 patients with 77 different KCNQ1 mutations, the dominant-negative ion channel dysfunction had a > twofold increase in the risk of cardiac events compared with those patients who had mutations with haploinsufficiency effects.[88] The same study showed that patients with transmembrane mutations had a significantly higher risk of cardiac events compared with C-terminus mutations. In addition, several recent studies showed that the dominant-negative KCNQ1-A341V mutation is associated with a particularly high clinical severity independently of the ethnic origin of the families.[89–91] The location of the mutation was also shown to be an important factor in LQT2 patients.[87] Patients with pore mutations in the KCNH2 gene were shown to have more severe ECG-signs and clinical manifestations occurring at an earlier age compared with subjects with non-pore mutations.[87] Additional genetic variants, however, may be present and may modify clinical severity of otherwise less severe mutations.[92]

9.8.2 LQTS Genotypes

Recent reports only assessing the life-threatening events ACA and SCD suggest that a specific genotype (LQT1-2-3) does not contribute significantly to the outcome after correcting for the clinical risk factors.[81–83]

9.8.3 Postpartum Period

The risk of syncope and sudden death is decreased during pregnancy. The postpartum period, however, is associated with a significant augmented risk of cardiac events in all types of LQTS, especially in LQT2.[93,94] The increased risk clusters in the 9-month period after delivery. In this period, cardiac events are more common in LQT2 (16%) than in LQT1 (<1%).[95,96] Nearly 10% of female probands experience their first event during this period.[93] The mechanisms by which the arrhythmias are generated are not clear. Many cofactors potentially play a role. Among these, changes in hormone balance (high levels of estrogens and progesterone), fatigue and sleep deprivation, stress, noise (crying of the baby), and anemia might play a role.[97] It is not known whether there is also an association with breastfeeding or the number of previous pregnancies.

Treatment with β-blockers should be continued during and directly after pregnancy. A close cardiac follow-up with serial ECGs and monitoring in a clinical setting after delivery is recommended when QT duration is significantly prolonged in comparison with prepregnancy values or when QTc exceeds 500 ms.[97]

9.8.4 Family History

The severity of symptoms in the proband does not predict the severity in affected family members.[98] A family history of SCD in a first-degree relative is not a significant predictor of outcome during childhood.[83]

9.9 Therapy and Prognosis

Data to guide the management of patients with LQTS have become available generally from large registries and referral centers and therefore may not reflect every patient since more severe cases may be overrepresented. Randomized trials of therapy are lacking because of the low prevalence of the LQTS and the variable penetrance of the disease.

General and genotype-specific lifestyle measures as well as the avoidance of QT-prolonging drugs are applicable to every LQTS patient. In addition to these obligate measures one often has to initiate β-blocker therapy, as most of the episodes of malignant ventricular arrhythmias are due to a sudden increase in sympathetic activity.[44] The efficacy of β-blockers has been recognized since the first description of the syndrome. However, one should remember that β-blocker therapy is not entirely effective in preventing malignant ventricular arrhythmias. Beta-blocker failure can be due to inadequate dosage, noncompliance, concomitant use of QT-prolonging medication, and/or incomplete effectiveness of β-blockers themselves. In addition, one has to know that there might be a period of extra risk after stopping β-blockers due to the up-regulation of β-receptors while on treatment. After initiating β-blocker therapy one has to decide whether this treatment will be safe enough for that patient in particular, because in some cases additional non-pharmacological interventions are necessary.[86]

The overall mortality in untreated, symptomatic LQTS patients is high and approached 50% over 10 years in early series.[99] Especially, remarkable is the mortality of 20% in the first year after the initial syncope.

9.9.1 Symptomatic Patients

9.9.1.1 General Lifestyle Measures

As stated LQTS-related syncope and death are most often adrenergically mediated (Table 9.6). Therefore, restriction of participation in competitive sports and/or athletic activities is generally recommended. However, it is not known whether this restriction should apply to patients, in which adrenergic stressors are not that prominent.

Table 9.6 Therapy in symptomatic LQTS patients

	LQT 1	LQT 2	LQT3
Lifestyle measurements, contraindicated medication, and gene-specific measurements	+	+	+
B-blocker therapy[100,101]	+	+	?
Pacemaker therapy (always in combination with β-blocker therapy)[104]		Pause-dependent TdP	Pronounced sinus bradycardia
Left cardiac sympathetic denervation (LCSD)[103]	Recurrent syncope despite β-blocker therapy Absolute contraindication for β-blocker therapy Electrical storm with ICD shocks		
ICD therapy[106]	Aborted cardiac arrest with or without therapy[a] Recurrent syncope despite β-blocker therapy and/or LCSD Absolute contraindication for β-blocker therapy in some cases Most LQT three patients (QTc > 500 ms) Special request patient or his/her parents, after thorough evaluation of the pros and cons		

TdP torsade de pointes

[a]Debatable in LQT 1 without β-blocker therapy (see Vincent et al.[101])

Cardiac and noncardiac drugs that block the I_{Kr} current and thereby prolong the QT-interval are contraindicated. A drug list of contraindicated medication can be found on www.azcert.org/medical-pros/druglists/drug-lists.cfm or on www.qtdrugs.org or on www.cardiogenetica.nl. Such a list should be given to all LQTS patients.

9.9.1.2 Beta-Adrenergic Blockade

Beta-adrenergic blocking agents represent the therapy of choice in symptomatic LQTS patients, unless specific and valid contraindications exist. Long-acting preparations such as propranolol retard, metoprolol retard, or nadolol are usually used in a maximal tolerated dose. Beta-blockers seldom result in excessive bradycardia, especially if the dosage is increased over several weeks very gradually.

Beta-blockers are extremely effective in LQT1 patients because the impairment of the I_{Ks} current makes them particularly sensitive to cathecholamines and very responsive to β-blockade. Priori and her colleagues demonstrated that cardiac events among genotyped patients receiving β-blockers occurred in 10% of LQT1 patients versus 23% in LQT2 patients and 32% in LQT3 patients during a mean follow-up of 5.2 years. Cardiac arrest occurred in 1.1%, 6.6%, and 14% for LQT1, LQT2, and LQT3, respectively.[100] These data and others showed that therapy with β-blockers alone is most often sufficient for LQT1 patients, also in case of aborted cardiac arrest as initial symptom.[101] Beta-blocker noncompliance and use of QT-prolongating drugs appeared responsible for almost all life-threatening "β-blocker failures" in LQT1 patients.[101] LQT2 and LQT3 patients are less well protected by β-blockers and for them (LQT3 in particular) additional therapies seem necessary in many cases.[100,102]

9.9.1.3 Left Cardiac Sympathetic Denervation

Left cardiac sympathetic denervation (LCSD) consists of the removal of the first four thoracic ganglia and can be performed quite safe without the necessity of thoracotomy. The major complication of the operation, the Horner's syndrome, can almost always be avoided. In approximately 30% of patients, a very modest ptosis will remain after the operation.

Peter Schwartz and his group reported their results on 147 LQTS patients who underwent LCSD in the last 35 years.[103] LCSD is associated with a significant reduction in the incidence of aborted cardiac arrest and syncope in high-risk LQTS patients. However, LCSD is not entirely effective in preventing cardiac events including sudden cardiac death during long-term follow-up. LCSD should be considered in patients with recurrent syncope despite beta-blockade and in patients who experience arrhythmia storms with an implanted defibrillator. Potentially LQT3 patients with major QTc prolongation and a personal or family history of events during rest or sleep should be considered for LCSD.

9.9.1.4 Pacemaker Therapy

Cardiac pacing as a therapy to prevent malignant ventricular arrhythmias in LQTS patients is seldom indicated. However, in some cases it can be highly effective.[104] For patients whose onset of TdP is preceded by a pause, as can be the case in LQT2, a pacemaker as adjunct to other therapy programmed with pause-preventing algorithms might be useful.[25] LQT3 patients with pronounced sinus bradycardia, which can be more prominent on β-blocker therapy, may benefit as well because the QTc lengthened disproportional during slow heart rhythms. Also in infants or young children with 2:1 AV-block pacemaker, implantation remains a reasonable choice as a bridge to the ICD.

However, if a pacemaker is considered, it is probably more logical to implant an ICD with adequate pacing modes. In addition, one should remember that cardiac pacing should always be combined with β-blocker therapy.

9.9.1.5 Implantable Cardioverter Defibrillator

Implantable cardioverter defibrillator (ICD) therapy is widely considered in LQTS patients at high risk for sudden death, but the clinical problem is how to select the appropriate patient for this therapy. It is commonly agreed that in the case of a documented cardiac arrest in a LQTS patient, either on or off therapy, an ICD should be implanted along with the use of β-blockers (Class I indication, level of evidence: A).[105] Recently, however, Vincent et al. showed that resuscitated LQT1

patients (in the absence of β-blocker) may do well on β-blockade alone.[101] Furthermore, implantation of an ICD with continued use of β-blockers can be effective to reduce sudden cardiac death in LQTS patients experiencing syncope and/or VT while receiving β-blockers (Class IIa, level of evidence: B).[105]

The indications for prophylactic ICD implantation in asymptomatic patients are less clear and less uniform. The guidelines indicate that implantation of an ICD with the use of β-blockers may be considered for prophylaxis of sudden cardiac death for patients in categories possibly associated with higher risk of cardiac arrest such as LQT2 and LQT3 (Class IIb, level of evidence: B).[105] Long-term follow-up studies are needed to help decision making. Nevertheless, there has been a major increase in the number of ICDs implanted in LQTS patients, probably in many cases not justified.

The available data from both the USA[106] ICD-LQTS Registry shows that the majority of the implanted patients has not suffered a cardiac arrest and, moreover, many had not even failed β-blocker therapy. One should not forget that the ICD does not prevent occurrence of malignant ventricular arrhythmias and that TdP are frequently self-terminating in these patients. In addition, ICD therapy is not without complications, such as infection and lead complications. The need for several battery and leads replacements, especially when implanted at young age, also remains a major clinical problem.

In our practice, the practical way to interpret the guidelines are as follows: (1) after a cardiac arrest (with or without other therapy) with possible exception for LQT1 patients not on β-blocker, (2) recurrent syncope despite full dose of β-blockade and possibly LCSD, (3) definite contraindication for β-blockers (exceptional), (4) specific patients with high risk characteristics based on age, sex, previous history, genetic subgroup (including sometime mutation-specific features), or presence of typical ECG signs indicating high electrical instability, (5) when requested by the patient or his/her parents after thoroughly explaining the risk/benefit ratio of an ICD and of alternative treatment modalities (β-blocker and LCSD).

When the indication for an ICD is established a decision needs to be made on the type of ICD. A factor to consider is the massive release of catecholamine, triggered by pain and fear that follows an ICD discharge in a conscious (young) patient, which may give rise to further arrhythmias and to further discharges. At the end of this dramatic vicious circle, the ICD can stop while the ventricular arrhythmia is not terminated. Specifically, to mitigate this effect, one can choose an ICD with special features like a long time prior to discharge to allow a spontaneous return to sinus rhythm after onset of TdP/VF. In addition, a period of relatively rapid pacing in the atrium after an appropriate shock could be of significance in preventing new ventricular arrhythmias and new shocks.[107] However, this latter algorithm is not standard in all ICDs available at this moment.

9.9.1.6 Genotype Specific Measures and Therapies

LQT1 patients should not be allowed to participate in competitive sports. Swimming is particularly dangerous, as 99% of the arrhythmic episodes associated with swimming were shown to occur in LQT1 patients.[40] Hence, swimming should be allowed only under guidance.

As LQT2 patients are at higher risk while awaking from sleep or rest by a sudden noise, it is recommended to remove telephones and alarm clocks from the bedroom, which can cause a startle reaction and initiate a polymorphic ventricular arrhythmia. In addition, it is sensible to wake children in the morning with caution. LQT2 patients are especially vulnerable when their potassium level is low and efforts should be made to maintain a serum potassium level > 4 mEq/L. In case of hypokalemia, oral K^+-supplements should be given.

Specific data regarding management of LQT3 patients are more limited because of the lower prevalence. There seems no benefit in restricting normal physical activity. An intercom system in the bedroom can be advised to detect a noisy gasping preceding death because of a progressive but slow fall in blood pressure as a consequence of the TdP.

The response to β-blocker therapy seems relatively poor in contrast to LQT1 and LQT2. Because LQT3 patients were shown to have excessive further prolongation of the QT-interval at slow heart rates, β-blocker therapy can even be harmful, although this has not been demonstrated convincingly.[102] Therefore, an early prophylactic ICD implantation might be considered in high-risk LQT3 patients. Sodium channel blockade represents a rational approach for a gene-specific therapy in LQT3, since the causative mutation precipitate

an increase in late sodium current via the Nav 1.5 sodium channel. Therefore, in some cases mexiletine can be given in addition to β-blocker therapy after tested efficacious in shortening QTc significantly by more than 40 ms.[102] However, long-term studies are not available and these drugs can therefore not replace the regular treatment options. Ranolazine, a novel drug that reduces late sodium channel current, might be of great potential in the future.[108]

9.9.2 Asymptomatic Patients

Asymptomatic LQTS patients should get the same general and specific lifestyle measures as their symptomatic counterparts. They should also have a list of drugs to be avoided. Given the fact that sudden cardiac death can be the first manifestation of LQTS patients it is considered necessary to prescribe a β-blocker to nearly all asymptomatic patients. However, there are some reasonable exceptions to make. Patients with a normal QTc (<440 ms), for example, have a very low risk and their treatment seems optional; the specific type of mutation they have could possibly influence the choice. In addition, LQT1 males older than 20–25 years, with a QTc < 500 ms, also carry a very low risk. In a minority of cases of asymptomatic patients a prophylactic ICD is indicated or wanted. These are patients with earlier mentioned high risk characteristics or with a special request.

9.10 Family Screening

Since the LQTS is a familial, monogenetic condition, all first degree family members should be screened for this potentially dangerous disease. First-degree family members are those who are sibling (brother or sister), parent, or child of the index patient. Given the autosomal dominant mode of inheritance, all of them have a 50% change of being an asymptomatic or symptomatic gene carrier.

Predictive genetic testing in first degree family members of a LQTS patient is a very important part of prevention, because it enables timely prophylactic measures and therapies in mutation carriers and therefore helps to reduce sudden death at young age. In addition, asymptomatic family members who are carriers may still pass on the mutation to 50% of their children, who in turn may have a more malignant phenotype due to the difference in penetrance.

In the evaluation of first degree relatives of a definitely affected LQTS proband (the index patient) with a documented pathogenic mutation in one of the LQTS-related genes, it is not acceptable to exclude LQTS based upon a normal QTc or a low "Schwartz score." One third of the asymptomatic gene mutation carriers have QTc values within the normal range. Using the "Schwartz criteria," a very low sensitivity of only 19% and a specificity of 99% for diagnosing LQTS in family members of proven LQTS patients were found.[109] Alternatively, these investigators found a cut-off value of the QTc of 430 ms a better way of screening of the family members with a sensitivity of 72% and a specificity of 86%. Therefore, molecular genetic testing (genotyping) is the only definitive diagnostic test for them.

Careful counseling prior to genetic testing is time-consuming but essential and therefore should preferably be done in a specialized multidisciplinary cardio genetic center, in close collaboration between a clinical geneticist and cardiologist. In case of children, a pediatric cardiologist together with psychosocial workers should work in a team to support the children and also the parents. Testing of asymptomatic persons or not yet diagnosed patients can have great influence on very different matters like psychosocial well-being, employment, or insurance issues. It has been documented that the testing procedure in LQTS patients leads to distress, which decreases over time. However, disease-related anxiety persists in the subgroup of carriers, which indicates the need for ongoing psychosocial care.[110]

Although there are no international guidelines, screening of children and prophylactic treatment when indicated has to start before life-threatening symptoms can be expected. This will depend on age and genotype. In the Netherlands we will screen children with LQTS type 1 long before the age of 5 and in particular before they start to swim. In families with LQTS type 2, children should be screened at age 8 and in the case of LQTS type 3 at the beginning of puberty.

As mentioned earlier one cannot exclude the diagnosis of LQTS in a family member on the basis of a normal ECG. If thereforethe person to be screened does not want a DNA-test, one has to deal with him or her as a potential patient with subsequent consequences

and permanent cardiological follow-up is indicated. The same applies for all family members of genotype-negative LQTS patients.

9.11 Summary

The congenital LQTS constitute a family of clinically heterogeneous entities, characterized by prolonged QT-intervals on the ECG and often abnormally appearing ST-T segments. The clinical course of the disease is time-dependent and age-specific with respect to gender differences. It predisposes especially young individuals without structural heart disease to malignant polymorphic ventricular arrhythmias, which in turn can lead to (recurrent) syncope, ACA, or even SCD. As such, the LQTS is one of the important causes of sudden cardiac death at age <45 year.

The molecular background of this hereditary disorder became apparent in 1995 and since then 12 different types of LQTS have been described. Hence, the congenital LQTS appears to be a genetically heterogeneous primary electrical heart disease with a monogenetic origin. It is part of the greater family of the genetic cardiac channelopathies.

The diagnosis of the LQTS relies mainly on the personal and family history of the patient in combination with more or less specific abnormalities on the electrocardiogram. In most cases (50–75%), the clinical diagnosis can be confirmed by DNA testing.

All symptomatic and asymptomatic patients with (suspected) LQTS have to receive certain lifestyle measures (general and genotype-specific) and must have cardiac follow-up visits on a structural basis in a specialized center in order to control therapy compliance. In addition, they should get a regularly updated list of prohibited QT-prolonging medications. The pharmacological treatment of patients with the LQTS consists principally of β-blockers, whether the patient is symptomatic or not. LQT1 patients can be treated with β-blockers as sole therapy with reasonable safety as long as they are fully compliant with their medications in a sufficiently high dose and avoid QT-prolonging drugs. It is important to realize that this can be a problem in some adolescents! In LQT2 and LQT3 patients β-blocker failures in arrhythmia prevention are more common and additional non-pharmacological treatment modalities (LCSD, pacemaker, ICD) are needed more often.

In addition to treating the index patient, one has to examine his or her first-degree relatives, who have 50% chance of being a mutation carrier or having the disease, in close collaboration with a clinical geneticist, psychosocial workers, and a pediatric cardiologist.

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