

Long QT syndrome: from genetic basis to treatment

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Abstract

The congenital long QT syndrome (LQTS) is a monogenic disorder, not as rare as it was originally estimated to be, mainly caused by mutations in genes encoding for ion channels. Molecular screening in this disease is part of the diagnostic process and this has already been recognized by current guidelines since 2006. However, very recently, two consensus documents have been published, with the recommendations for the use of genetic testing in the clinical evaluation of genetically transmitted arrhythmogenic diseases. Therefore, we devoted a specific section of the present review to the discussion of these two documents in relation to LQTS. The clinical presentation of the disease is typically characterized by a prolongation of the QT interval on the electrocardiogram (ECG) and by the occurrence of syncope or cardiac arrest, mainly precipitated by sympathetic activation. While the diagnosis of typical cases it is quite easy, borderline cases can be quite challenging and therefore the availability of diagnostic criteria is very useful to support the diagnostic process. Very recently, the LQTS diagnostic criteria have been updated and they are presented in the current review. Finally, the clinical management of LQTS patients is presented together with a schematic flow-chart and recent data coming from the LQTS-ICD European registry are illustrated. The last part of the review is dedicated at future perspectives and latest results on modifier genes and stem cells are presented.

Introduction

The congenital long QT syndrome (LQTS) is an uncommon genetic disorder¹ characterized by prolongation of the QT interval at the electrocardiogram (ECG), and by an increased risk of life-threatening arrhythmias.²

Two main variants of the disease have been described; the more common Romano-Ward syndrome (RW),^{3,4} with autosomal dominant transmission, and the rare Jervell and Lange-Nielsen syndrome (JLN), with autosomal recessive transmission associated with congenital neurosensorial deafness.^{5,6} Among channelopathies, LQTS is one of the better studied, and it is considered a good model to better understand the genetic basis of sudden cardiac death (SCD).⁷

Epidemiology

For many years LQTS was considered a very rare disease, with a prevalence assumed to be anywhere between 1/5000⁸ and 1/20,000,⁹ with most investigators settling for 1/10,000.¹⁰ However, no supporting data were available.

The first indication of the real prevalence of LQTS was published in 2009 and was based on the largest prospective study, ever performed, on neonatal electrocardiography.¹ An electrocardiogram was recorded in 44,596 infants at 3-4 weeks of age. Among them, 0.07% had a QTc greater than 470 ms, regarded as markedly prolonged by the European Task Force on Neonatal Electrocardiography¹¹ and 0.47% had a QTc between 451 and 470 ms. Molecular screening allowed the identification of a disease-causing mutation in 43% of the neonates with a QTc above 470 ms, and in 29% of those screened with a QTc between 461 and 470 ms (Figure 1). In total, 17 of 43,080 white infants were affected by LQTS, demonstrating a prevalence of at least 1:2534 in apparently healthy live births (95% CI, 1:1583 to 1:4350).¹

Clinical presentation and clinical diagnosis

The LQTS is typically characterized by a prolongation of the QT interval on the electrocardiogram (ECG) and by the occurrence of syncope or cardiac arrest, mainly precipitated by emotional or physical stress. The QT interval is considered prolonged if the QTc (QT corrected for heart rate) is greater than 440 ms; however, values up to 460 ms may still be normal among females. Despite exceptions, the longer is the QT and the greater is the risk for malig-

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nant arrhythmias. The Bazett's correction for heart rate (HR), despite some criticism related to hypercorrection and undercorrection occurring respectively at slow (< 60 bpm) and fast rates (> 100 bpm), remains the most commonly used formula to correct QT and it is very valuable in clinical practice.¹²

The clinical manifestations of the disease usually occur in otherwise healthy young persons, mostly children and teenagers and accordingly, LQTS is among the main causes of sudden cardiac death below age 20 years. The typical ventricular tachyarrhythmia, underlying the clinical manifestation of the disease, is torsade-de-pointes (TdP) that can be self-limiting or can degenerate into ventricular fibrillation and therefore causing cardiac arrest (CA)/SCD.¹² Besides QT prolongation, other ECG characteristics are typical of the disease.¹² The T wave can have several morphologic patterns, it is often biphasic or notched, and these abnormalities, usually more evident in the precordial leads, are very useful for the diagnosis (Figure 2A). Another typical but not common ECG feature is T wave alternans, a beat-to-beat alteration of the T wave, in polarity or amplitude. T wave alternans is a marker of major electrical instability and identifies patients at particular high risk (Figure 2B). The occurrence of sinus pauses, unrelated to sinus arrhythmia, is an additional warning signal. These pauses are often followed by the appearance of a notch on the T wave, and it is mostly from these notches that repetitive ventricular beats take off. Therefore the presence of T

wave alternans on the ECG tracing or the presence of sudden pauses followed by abnormal T wave morphologies, should prompt a correct diagnosis and the establishment or reassessment of therapy.

In view of the characteristic features of LQTS, for physicians aware of the disease the typical cases are easy to be diagnosed. However, borderline cases are more complex and require the evaluation of multiple variables besides clinical history and ECG. To support the diagnostic process, diagnostic criteria were proposed in 1985¹³ and subsequently updated^{14,15} (see also Schwartz PJ, Crotti L. *QTc behaviour during exercise stress test for the long QT syndrome. Circulation 2011;124:2181-4*). The new diagnostic criteria and the scoring system are listed in Table 1. Diagnostic criteria are based on electrocardiographic characteristics and on personal and family history. The patients are divided into three probability categories: i) ≤ 1 point = low probability of LQTS; ii) 1.5 to 3.0 points = intermediate probability of LQTS; and iii) ≥ 3.5 points = high probability of LQTS. These criteria are not useful to identify the so called *silent mutation carriers* who have a normal QT interval. For these individuals, molecular screening is essential.

Besides the typical Romano-Ward LQTS, worthy of discussion are the two most malignant form of long QT syndrome: the Jervell and Lange-Nielsen syndrome⁵⁻⁶ and the Timothy syndrome.¹⁶ The recessive JLN is characterized by the same cardiac phenotype observed in RW-LQTS, but with more severe manifestations, and by congenital deafness. Data on 187 patients with JLN have shown that nearly 90% of the patients have cardiac events and they become symptomatic much earlier than has been observed in other major genetic subgroups of LQTS.⁶ Additionally, conventional therapies may be less effective than in other LQTS patients. Timothy syndrome is an even more malignant and rare variant of LQTS, characterized by high mortality rate in the first years of life.¹⁶ At variance with other more common LQTS variants, the cardiac phenotype is frequently associated with non-cardiac manifestations (*i.e.* syndactyly, intermittent hypoglycemia, cognitive abnormalities, autism) and with congenital heart diseases.

Genetic basis

The genetic bases of long QT syndrome are known since the '90s. The three main disease-causing genes (*KCNQ1*, *KCNH2* and *SCN5A*), responsible for the vast majority of genotyped-positive cases were discovered between 1995 and 1996¹⁷⁻¹⁹ and they encode the α subunit of three ion channels, essential for the cardiac action potential. That is the reason why the

LQTS was very soon defined as a channelopathy.

KCNQ1 (KvLQT1) encodes the α subunit of the potassium channel conducting the I_{Ks} current. I_{Ks} is the slow component of the delayed rectifier current (I_K), the major determinant of the phase 3 of the cardiac action potential. When I_{Ks} is defective, the repolarization phase is prolonged and therefore there is a prolongation of the QT interval at the ECG (Figure 3). Mutations on *KCNQ1* are responsible for the LQT1 variant of the disease, which is the most prevalent one. Indeed, approximately half of the genotyped-positive patients carry a mutation on this gene.¹² Homozygous or compound heterozygous mutations of *KCNQ1* have been

associated with the recessive Jervell and Lange-Nielsen form that is characterized by a severe cardiac phenotype and by congenital neurosensory deafness, due to reduced I_{Ks} current in the inner ear.⁶

KCNH2 (HERG) encodes the α -subunit of the potassium channel conducting the rapid component of the delayed rectifier current (I_{Kr}). Loss of function mutations on this genes cause an impairment of the I_{Kr} current with a consequent prolongation of QT interval (Figure 3) and are responsible for the LQT2 variant of the disease. LQT2 is the second most common variant of LQTS, accounting for 35-40% of genotyped-positive cases.¹²

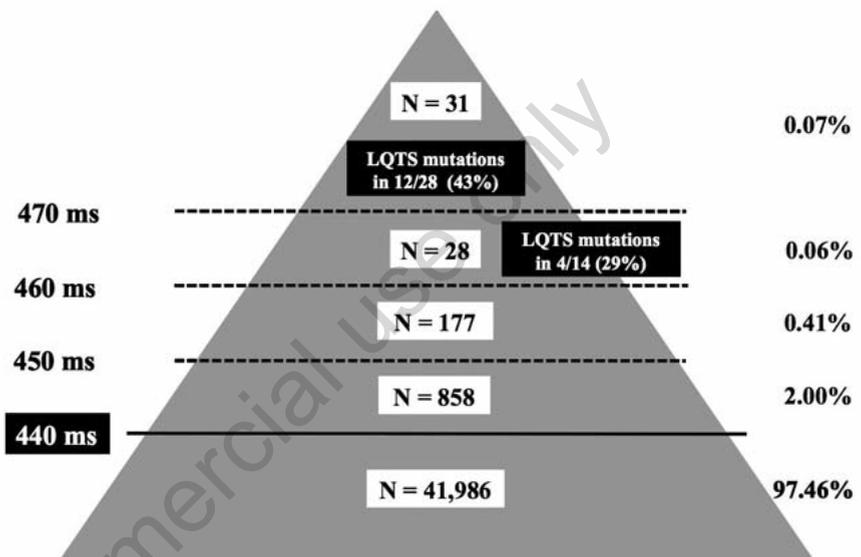


Figure 1. Distribution of the 43,080 Caucasian neonates among 5 groups according to QTc duration on the screening ECG and neonates positive at the genetic analysis.

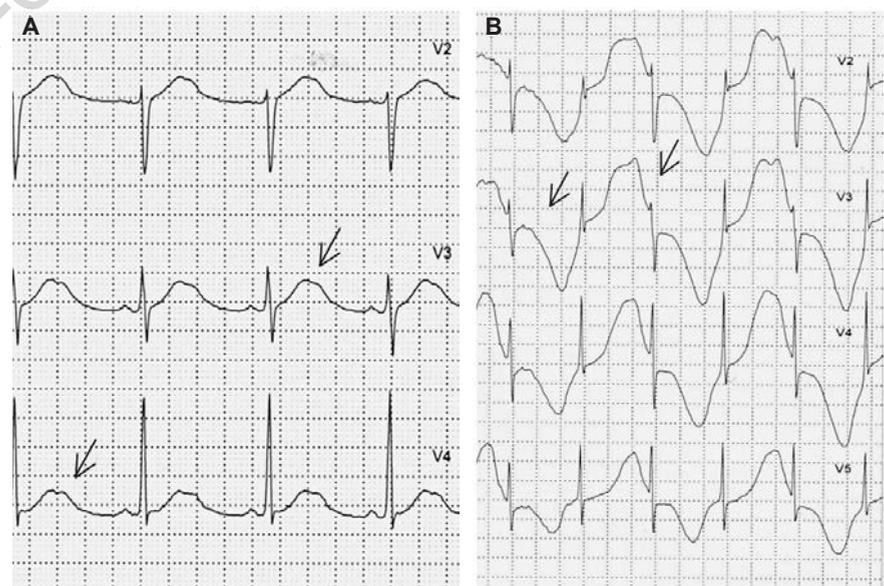


Figure 2. A) Example of notched T waves (arrows) in a 28-year-old long QT syndrome patient; B) T wave alternans (beat to beat change in polarity and morphology of T waves).

The third major LQTS gene is *SCN5A*, encoding the α -subunit of the cardiac sodium channel and conducting the depolarizing sodium inward current (I_{Na}). This gene is involved in the LQT3 variant of the disease, present in about 10-15% of genotyped-positive cases.¹² At variance with mutations on *KCNQ1* and *KCNH2*, mutations on *SCN5A* may produce a LQTS phenotype when they cause a gain of function of the channel. Indeed, it is only an increase in the Na^+ inward current which can prolong the action potential duration and consequently the QT interval²⁰ (Figure 3).

Following the identification of the first three LQTS genes, several others were identified, and up to now 13 is the total number of genes described in association with the disease (Table 2). However, each of these minor genes, with the exception of *KCNE1*, is responsible for less than 1% of genotyped-positive cases.

KCNE1 is located on chromosome 21 and encodes the β subunit (Mink) of the potassium channel conducting the I_{Ks} current.²¹ Heterozygous mutations in *KCNE1* may cause an uncommon variant of LQTS (LQT5),²² that account for approximately 2-3% of all genotyped-positive cases. However, homozygous or compound-heterozygous mutations have been described in association with the Jervell and Lange-Nielsen syndrome. *KCNE2* is also located on chromosome 21 and encode the β subunit (MIRP) of the potassium channel conducting the I_{Kr} current.²³ Mutations in *KCNE2* are associated with rare cases of LQTS (LQT6) and with cases of drug-induced long QT syndrome.

ANKB and *KCNJ2* genes have always been referred in association with LQT4 and LQT7; however, we believe that they should not be considered as part of LQTS, because they cause complex clinical disorders in which the modest prolongation of the QT interval is only a secondary epiphenomenon.¹²

LQT8 is a rare and malignant variant of LQTS, named Timothy syndrome, caused by mutations on *CACNA1C*, encoding a voltage-

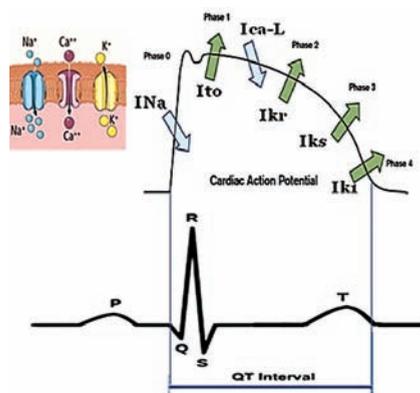


Figure 3. Major currents involved in cardiac action potential.

gated calcium channel. The disease is characterized by marked QT interval prolongation, often presenting with 2:1 functional atrio-ventricular block, macroscopic T wave alternans, and non-cardiac manifestations previously described. LQT8 is highly malignant, and 10/17 (59%) of the children reported by Splawski *et al.*¹⁶ died at a mean age of 2.5 years. Indeed, all the cases so far described had *de novo* missense mutations¹⁶ causing a reduced channel inactivation responsible for calcium overload, a well-known mechanism for tissue damage and arrhythmias induction.

Among the remaining LQTS genes, *CAV3*,

Table 1. 1993-2011 long QT syndrome diagnostic criteria.

Electrocardiographic findings*		Points	
A	QTc°	≥ 480 ms	3
		460-479 ms	2
		450-459 (male) ms	1
B	QTc° 4 th minute of recovery from exercise stress test ≥ 480 ms	1	
C	Torsade de pointes [‡]	2	
D	T wave alternans	1	
E	Notched T wave in 3 leads	1	
F	Low heart rate for age [§]	0.5	
Clinical history			
A	Syncope [‡]	with stress	2
		without stress	1
B	Congenital deafness	0.5	
Family history			
A	Family members with definite LQTS [^]	1	
B	Unexplained sudden cardiac death below age 30 among immediate family members [^]	0.5	

LQTS, long QT syndrome; *In the absence of medications or disorders known to affect these electrocardiographic features; °QTc calculated by Bazett's formula where $QTc = QT/RR$; [‡]Mutually exclusive; [§]Resting heart rate below the 2nd percentile for age; [^]The same family member cannot be counted in A and B. Score: ≤ 1 point: low probability of LQTS; 1.5 to 3 points: intermediate probability of LQTS; ≥ 3.5 points: high probability.

Table 2. Summary of long QT syndrome genes.

Gene	Locus	Syndrome	Frequency	Functional effect
<i>KCNQ1</i> (LQT1)	11p15.5	RWS, JLNS	40-55	Reduction of potassium current
<i>KCNH2</i> (LQT2)	7q35-36	RWS	30-45	Reduction of potassium current
<i>SCN5A</i> (LQT3)	3p21-p24	RWS	5-10	Increase sodium-channel current
<i>ANKB</i> (LQT4)	4q25-q27	RWS	<1%	Increase of AnkB expression
<i>KCNE1</i> (LQT5)	21q22.1	RWS, JLNS	2-3%	Reduction of potassium current
<i>KCNE2</i> (LQT6)	21q22.1	RWS	<1%	Reduction of potassium current
<i>KCNJ2</i> (LQT7)	17q23	AS	<1%	Reduction of potassium current
<i>CACNA1C</i> (LQT8)	12p13.3	TS	<1%	Increase of calcium current
<i>CAV3</i> (LQT9)	3p25	RWS	<1%	Increase inward sodium-channel current
<i>SCN4B</i> (LQT10)	11q23.3	RWS	<1%	Increase inward sodium-channel current
<i>AKAP9</i> (LQT11)	7q21-q22	RWS	<1%	Reduction of potassium inward current
<i>SNTA1</i> (LQT12)	20q11.2	RWS	<1%	Increase inward sodium-channel current
<i>KCNJ5</i> (LQT13)	11q24	RWS	<1%	Reduction of potassium inward current

RWS, Romano Ward syndrome; JLNS, Jervell Lange-Nielsen syndrome; AS, Andersen syndrome; TS, Timothy syndrome.

SCN4B and *SNTA1*, encode for sodium channel interacting proteins and therefore in the very few cases described, the final pathogenetic mechanism was an increase in the inward sodium-channel current.¹² While *AKAP9* and *KCNJ5*, encoding for Yotiao (a protein involved in the phosphorylation of *KCNQ1*) and for the kir3.4 subunit respectively, recognize as a final pathogenetic mechanism a reduction of potassium inward currents; I_{Ks} and I_{K1} respectively.

Recommendations for the use in clinical practice of molecular testing for long QT syndrome

Molecular screening in LQTS was recognized as a useful diagnostic tool by international guidelines in 2006.²⁴ Indeed, the ACC/AHA/ESC guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death clearly stated that *in patients affected by LQTS, genetic analysis is useful for risk stratification and for making therapeutic decisions. Although genetic analysis is not yet widely available, it is advisable to try to make it accessible to LQTS patients.* Additionally, the importance of screening family members, once a disease-causing mutation is identified in the proband, was highlighted.

More recently, two consensus documents have been published with the recommendations for the use of genetic testing in the clinical evaluation of genetically transmitted arrhythmogenic diseases.^{25,26} In both docu-

ments the genetic testing for family members of genetically confirmed LQTS cases was absolutely recommended, regardless of symptom status or baseline ECG;^{25,26} while for the probands the two documents present few differences. The main difference was related to the genes that need to be part of a diagnostic screening. In the Canadian joint position paper²⁵ *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1* and *KCNE2* were the genes that the authors suggested to include in the screening; while in the HRS/EHRA consensus statement only the three major genes were included.²⁶ Considering that the three main LQTS genes are responsible for the vast majority of genotyped-positive LQTS cases, we believe that the strategy suggested by HRS/EHRA consensus statement is more suitable for a simple diagnostic screening. However, it is important to stress the concept that molecular screening should always be guided by a careful clinical assessment of the patients. Indeed, if a JLN syndrome or a Timothy syndrome is suspected, the strategy of the screening should be modified accordingly. Additionally, with the advent of next-generation sequencing techniques and the availability of multiple gene panel, the screening approach also in clinical laboratories, could rapidly be changed.

Another slight difference between the two documents was related to the criteria of selection of the probands that should undergo a molecular screening. However, the underlying idea is exactly the same, that is to suggest molecular screening in patients with a clear diagnosis of LQTS, as it is obvious that the probability of success is strictly related to the probability of the disease.²⁷ However, for borderline cases the issue is more complex and

probably a clinical evaluation by experts, prior to receiving genetic testing, is recommended.²⁵

Clinical management

A flow-chart summarizing the clinical management of long QT syndrome at our Centre patients is provided in Figure 4.

General recommendations

All LQTS patients, regardless of symptoms, genotype and QT interval duration, should avoid all conditions that could further prolong the QT interval; therefore, facilitating the risk of life-threatening arrhythmias. These conditions are mainly two: i) the use of QT prolonging drugs (updated list available at www.torsades.org); ii) conditions favoring hypokalemia (*i.e.* vomiting, diarrhea, excessive perspiration and use of diuretics). Patients should always restore potassium with fruits and vegetables and/or with oral pharmacological potassium supplements, every time one of the conditions mentioned above should occur.

Physical activity in LQTS patients is allowed under controlled conditions; while competitive sports are contraindicated. However, differences in the risk profile can be observed according to the genotype. LQT1 patients are those at highest risk during physical activity and swimming is particularly dangerous;²⁸ LQT2 patients are at higher risk during emotional stress and this is an important component during competitions; LQT3 patients are at risk mainly in resting conditions when vagal activation is higher and therefore there is a debate about the indication to prevent these patients from doing competitive sports. Our view, not supported by data (difficult to obtain, given the restricted number of LQT3 patients), is that intense physical activity could be unsafe in these patients as well, because it progressively increases vagal tone, a factor that might increase the risk of life-threatening arrhythmias during sleep.

Finally, in LQT2 patients that are at particular risk after exposure to sudden noises during sleep or at rest, it is important not to place in the bedroom alarm clocks with loud sounds and telephones/mobile phones.²⁸

Asymptomatic long QT syndrome patients with prolonged QT

The treatment of choice in asymptomatic LQTS patients with prolonged QT interval is represented by β -blockers, whose efficacy in reducing LQTS-associated cardiac events is well established.¹³ However, not all β -blockers have the same efficacy. The two most effective ones are propranolol at the dose of 2-3 mg/kg/day (three times a day) and nadolol at the

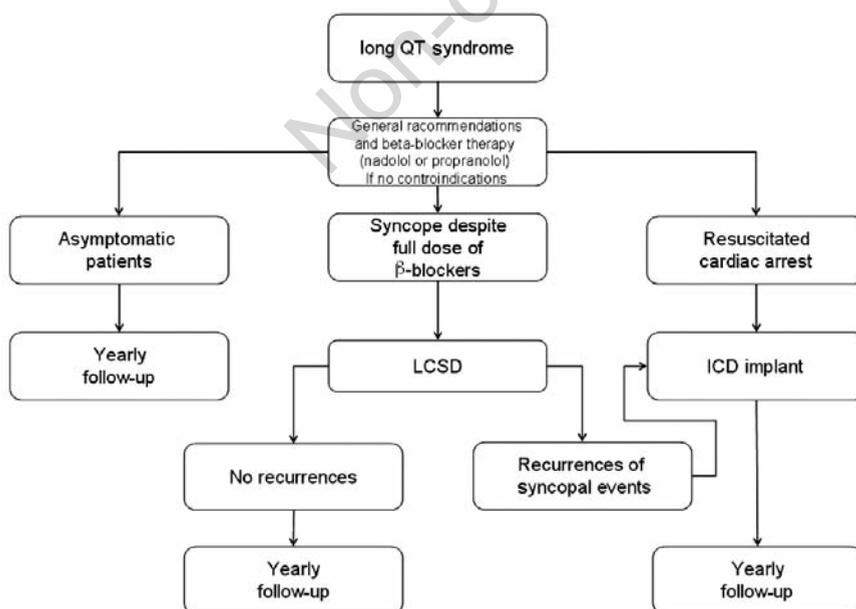


Figure 4. Flow-chart of long QT syndrome clinical management.

target dose of 1-1.5 mg/kg/day (two times a day); while metoprolol is definitely less effective and associated to tragic recurrences (Chockalingam P *et al.*, unpublished data). Importantly, to increase compliance, β -blockers should be progressively increased until the target dose, to avoid excessive fatigue and hypotension.

More aggressive treatments in asymptomatic LQTS patients are usually not necessary, with very few exceptions that will be described later in this review.

Symptomatic long QT syndrome patients

β -blockers are the first choice therapy also in patients with syncope events, and they are usually sufficient to obtain the control of symptoms. They are particularly effective in LQT1 patients, whose I_{Ks} impairment makes them highly sensitive to catecholamines. In two large studies^{29,30} mortality on β -blockers in this subgroup of patients was around 0.5% and the main cause of failure was non-compliance or the use of QT prolonging drugs.³⁰

Compared to LQT1, LQT2 and LQT3 patients have more cardiac events despite therapy;²⁹ however, the risk of sudden cardiac death on therapy remains low, with few exceptions. The main exception is represented by LQT3 patients with cardiac events in the first year of life, that have usually a very poor prognosis independently of treatment.³¹ In LQT3 patient, where the prolongation of the QT interval is linked to a gain of function of the sodium channel, the use of mexiletine³² should be considered in association with β -blockers. In our Centre the effectiveness of mexiletine is evaluated after administration of an oral acute test and add to β -blockers only if the QTc after the loading dose is shortened by more than 40 ms.

In case of recurrence of symptoms despite therapy, left cardiac sympathetic denervation (LCSD), should be considered, given its striking antifibrillatory effect.^{33,34} LCSD requires the removal of the first 3-4 left thoracic ganglia, while the cephalic portion of the left stellate ganglion is left intact to avoid Horner's syndrome. LCSD can be easily performed with an extrapleural approach;³⁵ while thoracoscopy³⁶ may represent an alternative surgical approach. Data published in 2004 on 147 high-risk LQTS patients who underwent LCSD showed a decrease by 91% of cardiac events after the procedure and in five patients with an ICD and multiple appropriate shocks, LCSD was able to decrease by 95% the number of appropriate ICD discharges.³⁷ LCSD is usually not suggested in asymptomatic patients; however few exceptions exist and typical cases are the patients not tolerating β -blockers or with a specific contraindication (*i.e.* severe asthma) in whom an antiadrenergic protection is needed.

Implantable cardioverter defibrillators (ICDs) represent the last line therapy for LQTS and should be reserved to patients at very-high risk. However, in the past ICDs have been over-used; an example of *defensive medicine*. In 2010 data on 233 LQTS patients implanted with an ICD, enrolled in the European LQTS-ICD registry, were published.³⁸ Surprisingly, a cardiac arrest before implantation occurred in less than 50% of the patients and 10% were completely asymptomatic before being implanted.³⁸ During a follow-up period of 4.6 ± 3.2 years, at least 1 appropriate shock was received by 28% of patients, and adverse events occurred in 25%. Appropriate ICD therapies were independently predicted by 4 main variables: i) age < 20 years at implantation; ii) a QTc > 500 milliseconds; iii) a prior cardiac arrest; iv) a cardiac event despite therapy. Indeed, appropriate shocks within 7 years, occurred in no patient with none of these factors and in 70% of those with all factors.³⁸ On the basis of these data and of our clinical experience we believe that logical candidates for ICD implants are all patients who survived a cardiac arrest (with the only exception of those who had a CA off therapy and in whom a reversible/preventable cause was clearly identified and corrected) and patients who continue to have syncope despite full-dose of β -blockers and LCSD, or full dose of β -blockers whenever the option of LCSD is not available or discarded after discussion with the patients. Exceptionally, an ICD could be considered also in asymptomatic patients with a QTc above 550 ms, who also manifest sign of high electrical instability (*i.e.* T wave alternans) despite full-therapy or other evidence of being at very high risk (*i.e.* very long pauses that might favour early afterdepolarization).³⁸

Asymptomatic long QT syndrome patients with normal QT

Patients with LQTS and a basal QTc below 440 ms represents approximately one fourth of the LQTS population.³⁹ They have a significantly lower risk for life-threatening events compared with phenotypically affected patients; however, their CA/SCD risk is more than 10-fold greater compared with unaffected family members.³⁹ A large study with the main focus on LQTS patients with a normal QT interval has been recently published, and the main determinants of arrhythmic risk in this subpopulation were identified. Surprisingly, only genetic factors (mutation characteristics and genotype) were able to influence the risk of CA/SCD in this subgroup of patients, whereas clinical factors, including QTc duration and sex, were associated with a significant increase in CA/SCD risk only in patients with prolonged QTc intervals.

In our Centre, patients with a positive molecular screening, but with a normal QT

interval are not always treated with β -blockers, but a careful clinical assessment, repeated during follow-up visits, is used, together with the genetic assessment, to evaluate the indication at β -blocker therapy.

Future perspectives

Modifier genes

Clinical heterogeneity and variable penetrance among patients with the long QT syndrome sharing the same disease-causing mutation is usually attributed to the coexistence of additional genetic and epigenetic factors that could have a role in modifying the clinical manifestation of the disease. The search for these *modifier factors* is object of an intense research activity, as they could provide from one side new clinical tools useful for the risk stratification of these patients and from another side they could unveil new mechanisms/pathways involved in arrhythmogenesis, useful for development of novel therapeutic approaches.

Some common genetic variants [single nucleotide polymorphisms (SNPs)] in cardiac ion channel genes represented the first good candidates as modifiers of the clinical severity of patients with a disease-causing mutation in these same genes. This hypothesis was proved in 2005, when we investigated a highly symptomatic LQTS proband with a mutation in KCNH2 (A1116V) and her relatives that despite carrying the same mutation were phenotypically mildly affected.⁴⁰ The clue of their difference was the coexistence in the proband, but not in the family members, of the common polymorphism *KCNH2-K897T* (present in 30% of caucasians) in trans with the mutation.⁴⁰ Heterologous expression studies demonstrated that co-expression of A1116V with K897T exaggerated the I_{Kr} reduction caused by the A1116V mutation, supporting the role of this common polymorphism as a major modifier of the clinical severity in this family.⁴⁰ Very recently, in another LQT2 family, the modifying role of K897T was further supported;⁴¹ however, we still do not know whether the effect of the K897T is limited to some *KCNH2* mutations or to all LQT2/LQTS patients.

Ideal populations to study the contribution of the so called *modifier genes* are populations of patients carrying the same disease-causing mutation (*i.e.* founder populations).^{42,43} Indeed, the disease-causing mutation remains the main determinant of the risk in LQTS and therefore an important confounding factor when searching for modifier genes in heterogeneous populations.^{42,43}

We are currently studying a large South African LQT1 founder population,⁴⁴ characterized by an unusual clinical severity⁴⁵ and we

have demonstrated that two common variants in the *NOS1AP* gene, encoding a nitric oxide synthase adaptor protein, are significantly associated with QT interval and clinical severity, being able to almost double the risk of life-threatening arrhythmias.⁴⁶ Subsequently, the role of *NOS1AP* as a genetic modifier of LQTS has been confirmed in a heterogeneous population of LQTS patients.⁴⁷

Despite very interesting and scientifically solid, these findings are not yet ready to enter the clinical practice as a more comprehensive knowledge of protective and favouring factors in the whole genome and further validations in large cohort of patients are probably needed.

Stem cells

Recent publications by Moretti *et al.*⁴⁸ and Itzhaki *et al.*⁴⁹ provided a powerful proof of principle demonstration that long QT syndrome can be modelled in induced pluripotent stem-cells (iPS cells) derived from patient's fibroblast. This is a great step-forward if we think that for this disease, all models existing so far have great limitations. Human cardiomyocytes are typically not available. Mammalian cells (*i.e.* CHO or HEK cells) used for testing the effect of specific mutations with patch-clamp techniques, completely lack to reproduce the complex system of an *in vivo* myocardial cell. Finally, in mice, the ion channels that contribute to the cardiac action potential are remarkably different from that of humans and for example I_{Kr} , the potassium current reduced in LQT2, is essentially absent in a normal mouse model.

Our expectation is that in the near future the iPS cells technology will be an accessible, convenient and cost-effective approach for gaining insights into the mechanisms underlying disease phenotype, for identifying modulating factors and testing new therapeutic approaches.

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