REVIEWS

Long QT Syndrome

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Abstract: The long QT syndrome is a potentially lethal electric disorder of the heart, characterized by a transient or permanent prolongation of the QT interval, carrying a risk for syncope, due to torsade de pointes and / or for sudden cardiac death, secondary to ventricular fibrillation. It comprises a congenital form and an acquired one. The congenital form has a genetic background, representing one of the several channelopathies, as an inherited dysfunction of a ion channel or of a regulatory protein is their common denominator.The acquired form has an extrinsic cause, usually a QT prolonging drug, an electrolyte imbalance or a bradyarrhythmia, possibly occuring in individuals with low penetrance of the congenital type. The genetic classification, the mechanisms for arrhythmogenesis, as well as the principles of management, tailored to the categories at risk, are presented.

Keywords: long QT, congenital, acquired, syncope, sudden death

Rezumat: Sindromul QT lung se caracterizează prin alungirea temporară sau permanentă a intervalului electrocardiografic QT, asociind risc de sincopă, secundară torsadei vârfurilor şi / sau de moarte cardiacă subită, secundară fibrilaţiei ventriculare. Există o formă congenitală şi una dobândită a sindromului. Forma congenitală reprezintă una dintre aritmiile de origine genetică, datorate disfuncţiei înnăscute a unui canal ionic din membrana celulei miocardice, mai rar a unei proteine reglatoare şi numite astfel canalopatii. Forma dobândită are o mulţime de cauze extrinseci, de obicei un medicament cu potenţial alungitor al QT, o diselectrolitemie sau o bradiaritmie. Sunt prezentate clasificarea genetică actuală a sindromului congenital, mecanismele aritmogenezei, precum şi principiile de tratament, adaptate stratificării riscului.

Cuvinte-cheie: QT lung, congenital, dobândit, sincopă, moarte subită

INTRODUCTION

The long QT syndrome (LQTS) consists of a transient or a permanent prolongation of the QT interval above the upper limit of normal, corrected for the heart rate, age and gender, predisposing to syncope due to torsade de pointes (TdP) type of ventricular tachycardia (VT) and / or to sudden cardiac death, secondary to ventricular fibrillation (VF)[1-3]. The LQTS has two forms: a congenital and an acquired one. The prevalence of the congenital form is estimated between 1/2000 and 1/3000 live births[4,5]. The acquired form is more common than the inherited one.

LQTS as a cause of sudden cardiac death

Most sudden deaths arise in connection with a structural defect of the heart, be it an ischaemic (80% of cases), a non-ischaemic or an acute mechanical one (aortic dissection, acute massive pulmonary embolism, interventricular septum rupture, blunt chest trauma). In a minority of cases (5-15%), including most of the cases of LQTS[6-9] no morphologic abnormality of the heart can be found (**Table 1**).

Congenital LQTS inside the genetic anomalies of the ion channels

So far, there is a spectrum of inherited arrhythmia syndromes arising from genetic defects in structures involved in the genesis of action potentials (AP), including congenital LQTS, Brugada syndrome, short QT syndrome (SQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), idiopathic VF, familial atrial fibrillation (AF) and at least some cases of the sick sinus sindrome (SSS) and of the progressive cardiac conduction defect (PCCD)[3,11]. Because a ion channel is usually the affected target, these diseases represent the so-called channelopathies[11,12], as a group (**Figure 1**). Either the increased efflux or the decreased influx of positive ions across the cell membrane, through defective channels within at least one myocardial wall layer, bring about short AP syndromes, as for example SQTS

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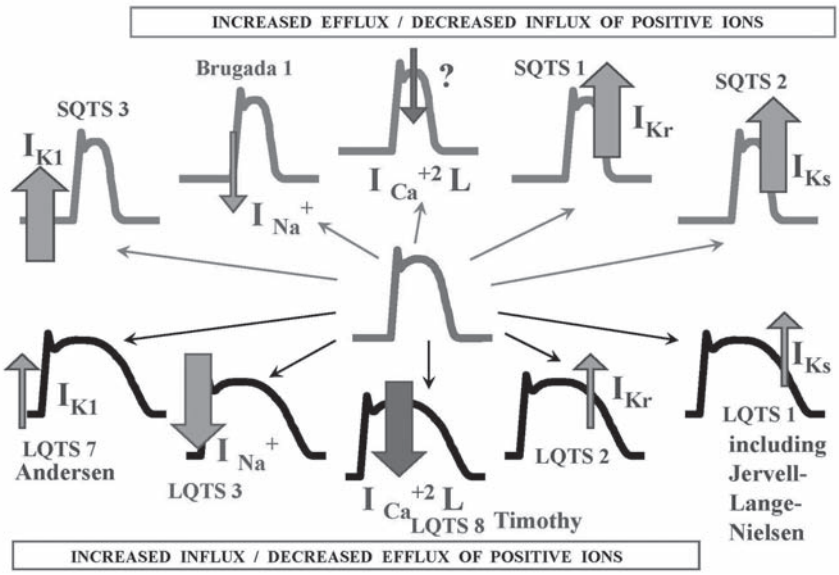

Figure 1. Congenital LQTS as a genetic channelopathy. LQTS = long QT syndrome; SQTS = short syndrome; IK1 = inward rectifier potassium channel; INa^{+} = sodium channel; ICa^{+2} L = L-type calcium channel; IKr = rapid component of the delayed outward rectifier channel; IKs = slow component of the delayed outward rectifier channel.

and Brugada syndrome. On the other hand, either the increased influx, or the decreased efflux of positive ion, again through defective channels, within at least one myocardial layer, give rise to long AP syndromes, including most of the types of LQTS[13]. A relationship between the traditional description and the current genetic classification of LQTS has been revealed. Accordingly, the autosomal dominant forms of the genetic types 1, 2, 3, 5 and 6 represent altogether the Romano-Ward syndrome, whereas the autosomal recessive forms of the failing subunits in the slow outward rectifier potassium channel IKs merge into the Jervell and Lange-Nielsen syndrome[3,12,14,15].

The genetic classification of congenital LQTS and the relationship to the risk profile

As yet, a number of 13 types of congenital LQTS have been characterized (**Table 2**). Together, they stand for 75-80% of all patients diagnosed with congenital LQTS. However, the first three ones discovered and therefore allocated as LQTS 1, LQTS 2 and LQTS 3 still remain the most common ones, comprising as a whole 95% of those with a genetic label and at least 70% of all congenital LQTS patients[5,16]. Most of the cases are the outcome of a direct change of the function (either a loss of function of the repolarizing channels, or a gain of function of the depolarizing ones), secondary to a mutation inside the gene coding for the synthesis of the channel subunit. The remaining cases usually derive from an indirect change of the ion channel function, due to a genetic alteration of a regulatory protein[5]. There is not just one, but several possible mutations for each type of congenital LQTS (over 700 mutations for all types of LQTS are described by now)[5]. Every one of them encodes for a region of the ion channel subunit or of the regulatory protein, resulting in different levels of infringement upon channel function and thus various degrees of clinical severity, even inside each type of LQTS, whatever it may be. The degree of the QT prolongation and its temporal variability, the shape of the T wave, the severity of the symptoms, along with some scarce anatomic features inside or outside the heart eventually result from the type of malfunctioning channel / protein and its mutation, as well as from the pattern of inheritance. For instance, among the most three common types of LQTS, IKs (LQTS 1) mutation has the least likely lethal cardiac event (when occurring) and INa^{+} (LQTS 3) mutation the most likely lethal one[3,17,18]. ICa^{+2}L (LQTS 8) mutations are presumably lethal in early life, where-

Table 1. Etiology of sudden death in an apparently normal heart (7-10)

Genetic alterations of the action potential, including: a) repolarization: long QT syndrome, Brugada syndrome, short QT syndrome, familial atrial fibrillation; b) automaticity: sick sinus syndrome (some cases); c) conduction: progressive cardiac conduction defect (Lenegre's disease)
Genetic anomalies of the intracellular calcium handling: catecholaminergic polymorphic ventricular tachycardia
Accesory pathways: Wolff-Parkinson-White syndrome
Ventricular tachycardia due to electrolyte disturbances: loop/thiazide diuretics, endocrine disorders: primary hyperaldosteronism, Addison's disease, hyper and hypoparathyroidism
Alcohol-induced ventricular tachycardia

Table 2. The genetic classification of the types of congenital long QT syndrome (4,5,13,54)

Genetic type of LQTS	Prevalence	Type of dysfunction loss/gain	Channel/ protein affected	Affected subunit	Encoding gene	Equivalence with traditional classification	
1	>90% of all genetically proved cases	loss	IKs	α	KCNQ1	Romano Ward	JLN 1
2		loss	IKr	α	KCNH2		
3		gain	INa^+	α	SCN5A		
4	Uncommon types: each_1% of all genetically proved	loss	*Ankyrin B		ANK2		
5		loss	IKs	B (MinK)	KCNE1	Romano Ward	JLN 2
6		loss	IKr	B (MiRP)	KCNE2		
7		loss	IK1	α	KCNJ2		
8		gain	ICa^{+2} L	α	CACNA1C		
9			Caveolin 3	INa^+ α gain	CAV3		
10		gain	INa^+	β	SCN4B		
11			**Yotiao	INa^+ α loss	AKAP9		
12			_1syntrophin	INa^+ α gain	SNTA1		
13		loss	IKAch	α	KCNJ5		

IKs = slow part of delayed outward rectifier potassium channel; IKr = rapid part of delayed outward rectifier potassium channel; INa+ = sodium channel; IK1 = inward rectifier potassium channel; ICa+2L = L-type calcium channel; JLN = Jervell-Lange-Nielsen; Alpha subunits of the channels contain the pore forming regions. * Ankyrin B anchors sarcolemmal proteins to the cytoskeleton; **Yotiao = protein within the adrenergetic dependent chain of activating IKr; alpha1syntrophin = cytoskeleton protein.

as IK1 (LQTS 7) has usually a lenient course[5,13,19]. Males bear higher risk than females in childhood whatever LQTS type might be[20], and throughout life in LQTS 3[10], while the opposite is true in all other instances for the first three types of congenital LQTS[21,22], as well as in the acquired form, a suppressive effect of the estrogens upon IKr channel being hypothesized[23]. However, the woman's risk does not lessen at menopause[24]. Channel conducting pathway (pore) region mutations in LQTS 2 harm more than non-pore coding ones[10,25], especially in men[26] and the homozygously affected individuals (e.g. Jervell-Lange-Nielsen) evolve worse than their heterozygous counterparts[15]. Moreover, in the so-called "concealed" cases (genotype-positive, but with normal corrected QT (QTc) at rest), transmembrane (non-pore) region mutations and the genetic type (LQTS 1 and LQTS 3) still carry a higher risk than that of non-affected persons, even if lower than in case of prolonged QTc[27]. Compared with baseline prolonged QTc individuals, in concealed cases the mutation itself and the genetic type of the syndrome are more powerful risk factors than the clinical descriptors (for example, female gender)[27]. The greater the number of distinct mutations in the same patients, the earlier the onset of the clinical picture may be.

The acquired LQTS

The same I_{Kr} channel involved in the pathogenesis of congenital LQTS can be affected by a manifold of drugs or non-pharmacological factors, producing the acquired LQTS[13,28,29] (**Table 3**). Hence, the sinus rhythm electrocardiogram of the acquired syndrome is usually alike to that of the congenital LQTS 2. Unlike the congenital

Table 3. Causes and risk factors for LQTS (10,28,29,31)

	LQTS	
	CONGENITAL	ACQUIRED
CAUSES	GENETIC DYSFUNCTION OF ION CHANNELS	QT PROLONGING DRUGS HYPOKALAEMIA MYOCARDIAL ISCHAEMIA MYOCARDITIS MITRAL VALVE PROLAPSE BRADYARRHYTHMIA SUBARACHNOID HEMORRAGE HYPOTHYROIDISM Ikr MINOR GENETIC DEFECT
RISK FACTORS	LQTS 1: PHYSICAL EXERCISE (especially swimming) LQTS 2: EMOTIONAL STRESS (especially NOISE) LQTS 3: SLEEP ANY LQTS: QT PROLONGING DRUGS, HYPOKALAEMIA	FEMALE GENDER RECENT ATRIAL FIBRILLATION CARDIOVERSION USING INTRAVENOUS IA/ III CLASS ANTIARRHYTHMIC AGENT HIGH MAINTENANCE DOSE (except QUINIDINE)

form, a noticeable cause for the acquired syndrome comes into sight. It can be one of the following: a structural cardiac abnormality, bradyarrhythmia, central sympathetic storm (secondary to subarachnoid hemorrhage), electrolyte imbalance (especially hypokalaemia and hypomagnesemia), hypothyroidism, or, more commonly, a QT prolonging drug[7,29,30], falling into one of several distinct therapeutic classes, all pertaining to an extensive and currently updating list (www.azcert.org) and blended together because of their ability to block the IKr current[29,31], or to inhibit the hepatic metabolism of IKr blockers[30]. Class IA or III antiarrhythmic drugs are often the culprit agents. Their propensity to

prolong QT interval and to increase the TDR is dose-dependent for almost all, except quinidine[32]. However, the amiodarone is perceived as a relatively safe drug. Its ability to perform a relatively homogenous prolongation of the APs and the attendant Na^+ and Ca^{+2}L channels blocking quality result in a lower risk for developing early afterdepolarizations (EADs) and thus for TdP, compared with other antiarrhythmics[31,33,34]. While safe in most instances, clustering of causes and of risk factors increases dramatically the risk for TdP, and this holds true for amiodarone, too[10,28,29,31] (**Table 3**). As a corollary to the acquired form of LQTS, the discrimination between causes and risk factors is sometimes elusive.

Issues regarding the measurement and the correction of QT interval

Both the measurement of the QT interval and its adjustment can be done either manually, or by dedicated software built in many present day electrocardiographic machines. Some cautions regarding the manual measurement must be observed, however. A stable isoelectric line and a fairly constant heart rate tracing should be looked for. Choosing the lead with the most clearly defined end of the T wave, from those leads where QT is expected to be the longest (V2 or V3) is recommended[35,36]. When a TU complex is present, the end of the T wave should be defined by the crossing point between the isoelectric line TP and the tangent line at the steepest downslope of the T wave final portion[35]. The RR interval used for correction is the RR interval just before the measured QT. The lead chosen as above is kept for subsequent comparisons. Still, one of the most widely used formula to adjust the QT for heart rate is Bazett s formula: $QTc = QT / \sqrt{RR}$, where QT and RR are measured in seconds[1,35,36], so it follows that Bazett QTc is measured in seconds$^{1/2}$. The fact that QTc is the slope of graph of the square root of RR interval explains the two big shortcomings of the formula, namely the underestimation of QTc (= QT overcorrection) in bradycardia (where the slope of the graph is gentle) and the overestimation of QTc (= QT undercorrection) in tachycardia (where the slope of graph is steep)[36,37]. Therefore, linear regression formulas are recommended to adjust for rate: $QTc = QT + 1.75 \times (HR - 60)$, where QT is measured in miliseconds and HR is the heart rate[35,36]. Moreover, age and gender must be taken into account, as well. The upper limits of normal for QTc values, as recommended by American Heart Association in 2009 are 0.45 sec for men and 0.46 sec for women, while the lower limit of normal is 0.39 sec for both genders[35]. To allow for age influence in children, the upper limit of normal of QTc for those younger than 6 months is 0.49 $s^{½}$ and 0.44 $s^{½}$ for other age groups, these last values being derived using Bazett formula[38]. Rate correction becomes useless in case of large RR variability (as for example AF), where the longest observed uncorrected QT should be reported accordingly.

The mechanism of arrhythmogenesis. The ECG diagnosis. "Concealed" cases

Different distributions of potassium channels within ventricular layers (particularly a minimal density of I_{Ks} in M-cells)[39] contribute to the normal transmural dispersion of AP durations and of the refractory periods (TDR). The M-cell has the longest AP and the subepicardial cell the shortest[40,41]. The intrinsic failure (seen in congenital LQTS) or the extrinsic impairment of an ion channel in the acquired form prolong the AP of the M-cell and exert variable influences upon the AP durations in the subendocardial and subepicardial layers[13]. On the one side, one can see the prolongation of QT interval, often associated, but not always, with an increased TDR. On the other side, the long AP of the M-cell allows the Ca^{+2}L channels to be reactivated during the same AP[39], promoting excessive Ca^{+2} storing in the sarcoplasmic reticulum. The ensuing release of intracellular Ca^{+2} further depolarizes the membrane (by activating Ca^{+2} dependent chloride current and Na^+/ Ca^{+2} exchange mechanism), giving rise to EADs. Besides further increasing the TDR, an EAD can manifest itself as the ventricular premature beat (VPB) triggering the TdP, if a certain voltage threshold is reached. Thereafter, the augmented TDR favors the perpetuation of the tachycardia by the reentry mechanism[30,33,42,43]. On the electrocardiogram (**Figure 2**), the TdP associated with

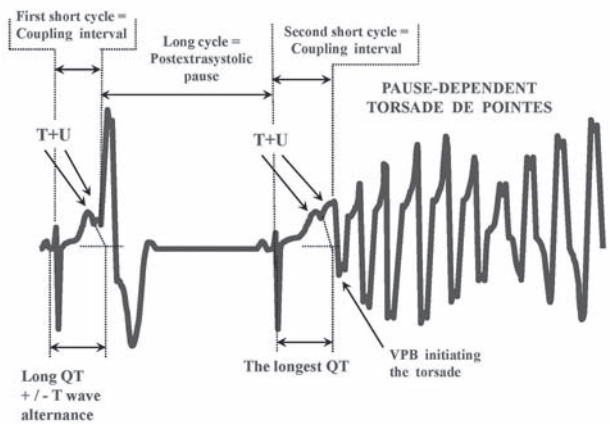

Figure 2. The onset of the pause-dependent torsade de pointes. VPB = ventricular premature beat. Data in references 30,32.

the acquired LQTS and with the congenital LQTS 3 is labeled pause-dependent TdP. Herein it is initiated by a typical sequence, called "short-long-short cycle"[32]. The first short cycle is represented by the coupling interval of a VPB. The long cycle is the compensatory pause following that VPB, whereas the second short cycle is the coupling interval of the first beat of the tachycardia. In sinus rhythm, QT interval is already long and after the pause it becomes longer[32]. The twisting pattern of the spikes of QRS complexes around the baseline is explained by a periodic rotation in space of the spiral wave of the tachycardia[33]. Depending on the amplitude of the EAD and on the value of the TDR, several electrocardiographic scenarios may follow: T wave / TU complex alternance, VPB bigeminism and the TdP. A bidirectional type of VT may also be seen in LQTS 7 (Andersen)[11,44]. Usually, the TdP is recurrent and self limited, but sometimes (less then 10% of cases) degenerates into VF[11,32]. TdP in congenital LQTS 1 and 2 may begin without the typical "short-long-short" sequence[45]. It appears and persists during the sympathetic stimulation in LQTS 1, but only at the beginning of sympathetic release in LQTS 2[46]. Forms of the LQTS where the AP prolongation is quite homogenous have a relatively benign history, with a low prevalence of TdP (LQTS 7 Andersen[13], or cases with mild prolongation of QTc under amiodarone as sole risk factor). There has been depicted a characteristic pattern in sinus rhythm for each of the main three types of congenital LQTS, as follows: LQTS 1 has a broad based T wave, LQTS 2 has a low amplitude T wave (sometimes notched, too), whereas LQTS 3 has a narrow based T wave[1,2,3,11]. The acquired LQTS shows often a pattern similar to that of congenital type 2. Unlike in other types of congenital LQTS, an exaggerated U wave has been described in LQTS 7 (Andersen)[10,11,47]. Narrow-based T waves (alike those in LQTS 3) and sometimes giant negative T waves in precordial leads are seen in Timothy syndrome[48]. Aside from the QT prolongation itself and its dispersion in surface leads, the Tpeak-Tend interval in precordial leads (or, more generally, the interval from the peak/nadir of the first component of the T wave to its end) is considered to be a non-invasive indicator of TDR[33], while a fragmented QRS is suggested to be a risk indicator for torsade in acquired LQTS, too[49]. The electrocardiogram of certain cases of congenital LQTS behaves somehow alike to that of the acquired form, as both show a significant variability of QTc over time. It happens especially in heterozygous carriers of IKs mutations in LQTS 1 and LQTS 5[4]. The temporal variability of QTc in congenital LQTS can reach 47 ± 40 ms, including an incidental normal QTc and still carrying a small risk for TdP[50]. The term "concealed" was coined to label these cases, which may account for 36% of all cases of LQTS 1, 19% of all cases of LQTS 2 and 10% of cases of LQTS 3[46]. The concealed cases fall under the heading of a more general phenomenon of incomplete penetrance of all genetic disorders of the ion channels, while standing for a difficult diagnosis. Persons with the acquired form of LQTS may well be recruited from the bulk of concealed cases. The electrocardiographic diagnosis of concealed LQTS relies upon time (ambulatory Holter recordings) and space follow-up (multiple lead body surface ecg), but provocative tests (exercise stress testing, epinephrine stress) may be needed, as some cases of Brugada syndrome need provocative diagnostic testing (Na^+ channel blockers in this case), too[4,46]. Roughly speaking, the concealed cases of channelopathies are endowed with a risk falling between the risk of spontaneously manifest cases and that of non-carriers, and LQTS does not break this foregoing record[6,51].

The diagnostic criteria for congenital LQTS presented elsewhere, have been released in 1993, building up a probability diagnosis, founded upon electrocardiographic, personal history and family history elements[1,52]. Albeit stated before the genetic knowledge breakthrough, they still hold useful, either when genetic diagnosis is out of reach, or as a complementary diagnosis to the genetic work-up done for concealed cases.

Structural abnormalities associated with LQTS

Most cases of congenital LQTS have a normal morphological heart and no extracardiac abnormality. The first historically known abnormality was the sensorineural deafness in Jervell and Lange-Nielsen syndrome[14,15,53]. Since the beginning of the genetic Odyssey, two other types of LQTS joined the puzzle. One of them is the Andersen-Tawil syndrome (LQTS 7), whose array of features includes a potassium-sensitive periodic paralysis (triggered by exercise or by glucose ingestion), hypertelorism, widened nose base, low-set ears, highly convex palate, small lower jaw, small hands and feet, with syndactyly of the toes[5,11,13,47,54,55]. The other one is Timothy syndrome (LQTS 8), featuring autism, baldness, low-set ears, small upper jaw, dysmorphic teeth, syndactyly both in fingers and in toes, along with congenital heart defects, such as patent ductus arteriosus, patent foramen ovale, ventricular septal defect, tetralogy of Fallot. Timothy syndrome may include a functional 2/1 atrioventricular block, due to an exceedingly long QT interval[5,19,48]. Even if the acquired LQTS is fun-

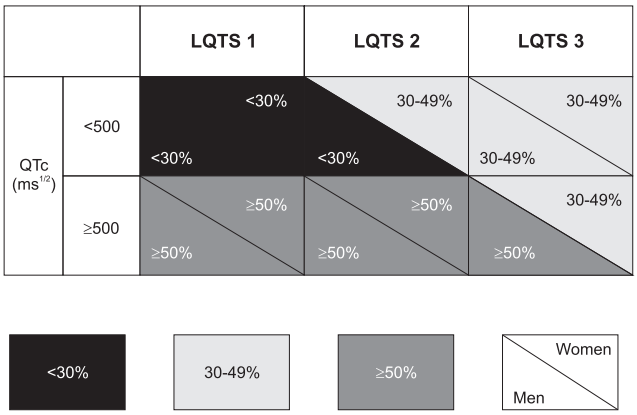

Figure 3. The risk stratification for a first cardiac event in life, before age of 40 and without treatment in congenital LQTS types 1, 2 and 3, depending upon QTc value and gender. High-risk is superior to 50%, medium-risk lies between 30 and 49%, whereas low-risk is inferior to 30%. Data in reference 21.

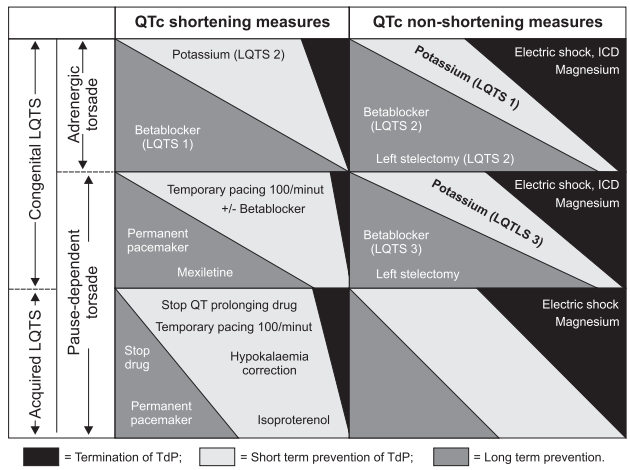

Figure 4. Management of LQTS.

damentally an electric disorder, a particular anatomic substrate can occasionally be found (myocardial infarction, myocarditis, or a mitral valve prolapse).

Risk stratification

Congenital LQTS: 1) High risk for relapse: patients with personal (not family)[10,56] history of aborted cardiac arrest[22,57,58], or recent and / or repetitive syncope (especially when first event early in life[59,60] and / or on treatment[61]); 2) Categories at risk for a first cardiac event in life, in the next 5 years (syncope / cardiac arrest / sudden cardiac death) before the age of 40 and without being treated[1,21] (**Figure 3**): 2a) high risk ≥50%: LQTS 1, 2 and 3 with QTc ≥ 500 ms 1/2, apart from the woman with LQTS 3; 2b) low risk <30%: LQTS 1 and 2 with QTc <500 ms$^{1/2}$, apart from the woman with LQTS 2; 2c) medium risk 30-49%: the LQTS 3 woman with QTc ≥500 ms$^{1/2}$, the LQTS 2 woman with QTc <500 ms $^{1/2}$ and all LQTS 3 patients with QTc <500 ms$^{1/2}$; 3) risk increased for the woman with LQTS 2 in the first few months after a childbirth, whereas pregnancy is relatively safe[62]. While being well above the upper limits of normal for both genders, the 500 ms$^{1/2}$ QTc is a cut-off value for high risk individuals[37,50]. Acquired LQTS: any clustering of causes and risk factors, especially if symptomatic before.

Principles of management of the LQTS

As not all syncopes in a patient having LQTS are automatically due to TdP, the treatment of any form of LQTS is essentially the prevention and termination of TdP and consequently the prevention of sudden cardiac death. Shortening of QT interval is neither the main goal, nor is always possible. The long-term prevention of TdP in congenital LQTS is attempted by a) avoiding the known risk factors (**Table 3**), b) safeguard against sympathetic stimulation (betablockers, the mainstay of the treatment[1], are mandatory and highly efficient in all cases of LQTS[13,20,63], moderately efficient in LQTS 2, including the pregnancy[62] and asthma patients[64], but are questionable in LQTS 3[11,65] and in JLN patients[15]) and c) the possible reduction of the dispersion of refractoriness (by left superior cervico-thoracic sympathectomy, in selected cases[66]). The long-term prevention of TdP in acquired LQTS is obtained by in-hospital monitoring of the first days of IA / III antiarrhythmic drugs[32] and by removal and / or treatment of any identified cause[28,32] (**Table 3**). The prevention of a TdP dependent on a bradyarrhythmia benefits from the bradyarrhythmia treatment10 for any causal LQTS, be it acquired or congenital type 3. Potassium allows the short-term prevention of TdP[10], not only in hypokalaemia-induced case, but also in congenital LQTS (here even if no hypokalaemia documented). Stopping TdP in any congenital or acquired case is achieved with intravenous magnesium sulphate and delivery of external electric shock (if TdP episode prolonged or degenerating into VF)[32]. Moreover, tachyarrhythmia episodes can also be terminated by the implantable cardioverter-defibrillator (ICD) a patient with congenital LQTS has already received[67]. Some of the aforementioned methods shorten the QTc in sinus rhythm, while others do not (without meaning being less efficient). A synthesis of the available management methods is presented in **Figure 4**.

Recommendations for prophylactic management of the congenital LQTS, according to the categories at risk[10]

All patients must avoid known risk factors (strenuous exercise in LQTS 1, emotional stress and noise in

LQTS 2, and any reversible risk factor for the acquired cases) (class I recommendation). Betablockers are recommended (class I) for any patient with electrocardiographic diagnosis and QTc ≥500 $ms^{1/2}$ (including the pregnant woman) and they are useful (class IIa recommendation) for the patient with QTc <500 $ms^{1/2}$. The ICD is recommended (class I) for the secondary prevention of sudden cardiac death after an aborted cardiac arrest, it is useful (IIa) in the secondary prevention of both syncope and TdP and it is suggested (IIb) for the asymptomatic patient carrying a high or medium risk (≥30%)[68]. The ICD must be associated with the betablocker. The left superior cervico-thoracic sympathectomy is suggested (IIb) for unabating symptoms while on betablocker plus ICD.

Conflict of interests: The author declare that no conflict of interest exists.

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