Congenital long QT syndrome in children

Kongenitalni sindrom produženog QT intervala kod dece

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Apstrakt

Sindrom produženog QT intervala (engl. *long QT syndrome, LQTS*) je poremećaj repolarizacije komora miokarda koji se odlikuje produženjem QT intervala na elektrokardiogramu (EKG) i povećanim rizikom za nastanak ventrikularnih tahiaritmija i kardiogenih manifestacija. Može da bude stečeni ili kongenitalni, koji predstavlja skup kanalopatija usled mutacija u nekom od 15 do sada identifikovanih gena. Najčešći oblici kongenitalnog sindroma su LQT1, LQT2 i LQT3. Zbog produženja repolarizacije i, posledično, celog akcionog potencijala, stvaraju se uslovi za nastanak rane naknadne depolarizacije i izraženije transmuralne disperzije repolarizacije koje su, pojedinačno ili udruženo, osnova za nastanak *Torsades de pointes* ventrikularne tahikardije. Sindrom produženog QT intervala se klinički manifestuje palpitacijama, sinkopom, srčanim zastojem ili naprasnom srčanom smrću, a može da bude i asimptomatski. Provocirajući faktori za nastanak tegoba su specifični za određeni genotip. Ispitivanje LQTS obuhvata ličnu i porodičnu anamnezu sa naglaskom na karakteristične podatke (česte sinkope, iznenadna srčana smrt u porodici, nasledne aritmije), EKG u miru, test opterećenja i genetske analize, kao i druge dodatne metode (serijski EKG zapisi, 24h EKG holter, epinefrinski test). Za kliničko postavljanje dijagnoze koristi se Švarcov (Schwartz) skor, a kriterijumi za definitivno postavljanje dijagnoze zavise od Švarcovog skora, dužine QT intervala, postojanja mutacije i kliničke slike. Lečenje se zasniva na promeni životnih navika i terapiji β-blokatorima, a druge mogućnosti su ugradnja implantabilnog kardioverter-defibrilatora, permanentnog pejsmejkera ili hirurška simpatektomija. Sindrom produženog QT intervala je jedan od potencijalnih uzroka iznenadne srčane smrti koja čini 90% iznenadnih smrti mladih sportista. Kod dece sa LQTS preporuke za bavljenje sportom proizilaze iz preporuka za odrasle i podrazumevaju vrlo stroga ograničenja. Dalja istraživanja biće usmerena na bolje razumevanje genotip-fenotip korelacije kongenitalnih LQTS i očekuje se da će pružiti nove personalizovane terapijske mogućnosti i saznanja o ređim tipovima ovog sindroma, kao i jasnije preporuke za bavljenje fizičkom aktivnošću kod dece sa LQTS.

Ključne reči: sindrom produženog QT intervala, deca, genetika, fizička aktivnost

Abstract

Long QT syndrome (LQTS) is a cardiac repolarization disorder characterized by prolonged QT interval on the electrocardiogram (ECG) and increased propensity to ventricular tachyarrhythmias and cardiac events. LQTS might be acquired or congenital, which presents a group of channelopathies that occur due to mutation in one of 15 so far identified genes. The most frequent types of congenital LTQS are LQT1, LQT2 and LQT3. Prolonged or delayed repolarization leads to the increase of action potential duration which predisposes early afterdepolarization, as well as the amplification of transmural dispersion of repolarization, both contributing to the development of *Torsades de Pointes* ventricular tachycardia. Clinical manifestations of LQTS are palpitations, syncope, aborted cardiac arrest or sudden cardiac death, but it can also be asymptomatic. Trigger factors for symptoms are specific for certain genotype. LQTS examination includes thorough clinical and family history focused on distinctive data (repeated syncopes, cases of sudden cardiac death in the family, hereditary arrhythmias), resting ECG, exercise stress testing and genetic analysis, with additional methods (serial ECG records, 24h ECG Holter, epinephrine test). Clinical LQTS diagnosis is based on Schwartz's scoring system, while the criteria for final diagnosis of LQTS depend on Schwartz`s score, QT interval duration, presence of pathogenic mutation and clinical symptoms. Treatment approach begins with lifestyle modifications and β-blockers therapy, while other options include implantable cardioverter-defibrillator, permanent pacemaker or surgical sympathectomy. Sudden cardiac death is the reason of 90% of sudden deaths in young athletes, while LQTS is one of its causes. Recommendations for physical activities in children with congenital LQTS arise from the ones for adults and they presume very strict limitations. Further researches are expected to advance the understanding of genotype-phenotype correlation of congenital LQTS and enable eventual genetically-guided personalized treatment, novel insight into rare LQTS types, as well as more precise recommendations for physical activity of LQTS children.

Key words: long QT syndrome, children, genetics, physical activity

Introduction

Long QT syndrome (LQTS) is a cardiac repolarization disorder characterized by prolonged QT interval on the electrocardiogram (ECG) and increased propensity to ventricular tachyarrhythmias (*Torsades de pointes* (TdP) tachycardia and ventricular fibrillation (VF)) (figure 1a). It can be asymptomatic or clinically manifested as palpitations, syncope, aborted cardiac arrest (ACA) or sudden cardiac death (SCD) (1). LQTS might be congenital or acquired, with potential causes including myocardial ischemia, cardiomyopathy, certain drug consumption (antiarrhytmics, antibiotics, antidepressives, antipsychotics, etc), hypokalemia or hypomagnesaemia (2). Congenital LQTS presents a group of monogenic, predominantly autosomal-dominant (A-D) channelopathies or other proteinopathies, denominated as LQT1-LQT15, according to 15 so far identified genes known to be associated with LQTS (table 1) (3). The estimated prevalence of 1:2000 subjects is supposed to be even greater on the behalf of subclinical forms, while about 50% of eventually symptomatic LQTS patients experience their first cardiac event by the age of 12 (4). Also, in 10% of cases of sudden infant death syndrome (SIDS) is proven a LQTS-gene mutation (5).

Genetic and molecular basis

In 75% of non-acquired LQTS is found a causal mutation (6), out of which 85% are inherited and the remaining occur *de novo* (7). The most common forms are LQT1, LQT2 and LQT3, constituting about 90% of genetically proven cases (1). These mutations cause alterations in specific ion channels which participate in action potential, leading to the delay of repolarization process.

LQT1, the most common form present in about 45% of genotyped patients, arises from the loss of function in KCNQ1 gene, which encodes α-subunit of the slow activating potassium channel, responsible for slow delayed rectifier potassium current (IKs) (7). LQT2, with frequency of 35-40%, stems due to mutation in KCNH2 gene, encoding the α-subunit of potassium channel responsible for rapid delayed rectifier potassium current (IKr) (7). There are two mechanisms mediating the reduction of repolarizing current and ensuing delayed repolarization in potassium channel mutations: 1) trafficking defect, when mutant subunits are not transported or incorporated properly in tetrameric channel; and 2) formation of defective channels, resulting in >50% reduction in channel current (8). On the other hand, LQT3 results from gain-of-function mutation in SCN5A gene which encodes rap-

Table 1. Congenital LQTS genes, affected proteins and ion currents (3).

LQTS type	Gene	Protein	Protein function	Current	Frequency (%)
LQT1	KCNQ1	Kv7.1	α-subunit IKs channel	↓ IKs	40–55
LQT2	KCNH2	Kv11.1	α-subunit IKr channel	↓ IKr	30–45
LQT3	SCN5A	Nav1.5	α-subunit INa channel	↑ INa	5–10
LQT4	ANKB	Ankyrin	Adaptor protein	↓ Coordination of Ncx, Na/K ATPase	Rare
LQT5	KCNE1	MinK	β-subunit *I*Ks channel	↓ IKs	Rare
LQT6	KCNE2	MiRP1	β-subunit IKr channel	↓ IKr	Rare
LQT7	KCNJ2	Kir2.1	α-subunit IK1 channel	↓ IK1	Rare
LQT8	CACNA1C	Cav1.2	α-subunit *I*CaL channel	↑ ICa	Rare
LQT9	CAV3	Caveolin 3	Component of caveolae (co-localizes with Nav1.5)	↑ INa	Rare
LQT10	SCN4B	β4-subunit	β-subunit INa channel	↑ INa	Very rare
LQT11	AKAP9	Yotao	Mediates Kv7.1 phosphorylation	↓ IKs	Very rare
LQT12	SNTA1	Syntrophin-α1	Regulates INa channel function	↑ INa	Very rare
LQT13	KCNJ5	Kir3.4	Subunit KACh channel	↓ IK-ACh	Very rare
LQT14	CALM1	Calmodulin 1	Calmodulin	Dysfunctional Ca^{2+} signaling	Rare
LQT15	CALM2	Calmodulin 2	Calmodulin	Dysfunctional Ca^{2+} signaling	Rare

idly inactivating sodium channel, so the channel fails to close properly; continuous inward leakage of sodium ions prolongs plateau phase and therefore delays repolarization (8).

Mechanisms of ventricular tachyarrhythmias development

Ventricular myocardium is comprised of at least three electrophysiologically and functionally distinct cell types - epicardial, M and endocardial cells, which show electrical heterogeneity in the form of transmural dispersion of repolarization (TDR), under baseline conditions (9). Prolonged or delayed repolarization leads to the increase of action potential duration (APD) which, due to higher intracellular concentration of calcium, during phases 2 or 3 of action potential, predisposes early afterdepolarization (EAD) (10). Agents that prolong APD produce preferential prolongation of the M cell action potential than of the epicardial or endocardial cells, leading to the amplification of TDR (11). That creates a vulnerable window for the development of reentry phenomenon as well as EAD, both contributing to the development of TdP (figure 1b) (11). Depending on the duration, TdP can progress to ventricular fibrillation or cardiac arrest.
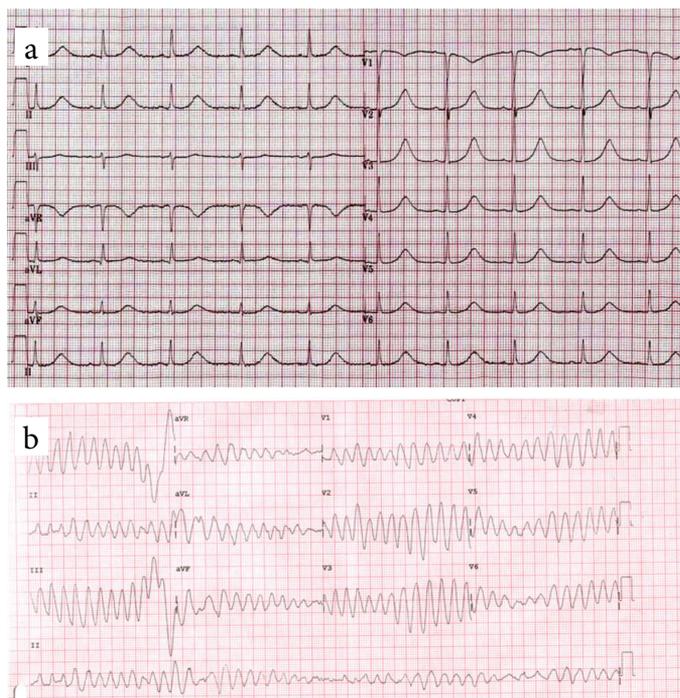

Figure 1. Representative ECG findings: a) prolonged QT interval; b) Torsades de pointes.

Clinical presentation

The most frequent symptoms of LQTS are palpitations and syncope. However, it can be an accidental ECG finding in an asymptomatic patient, while ACA or SCD as the first manifestation of the disease occur in 1-3% (3). Clinical presentation depends on inheritance pattern, genetic polymorphism, penetrance and modifier genes, as well as the age, gender, environmental factors and therapy (3).

Congenital LQTS can be phenotypically classified into four syndromes. The most common is A-D inherited Romano-Ward syndrome, which may result from a mutation in any of LQTS genes and it has the widest range of cardiac manifestations (7). Jervell and Lange-Nielsen (JLN) syndrome is a rare autosomal recessive (A-R) disease caused by homozygous mutation in KCNQ1, associated with congenital deafness and very severe form of LQTS (12). Andersen-Tawil syndrome, known as LQT7, is a rare A-D condition characterized by hypokalemic periodic paralysis, ventricular tachyarrhythmias and a variety of dysmorphic features (13). Tymothy syndrome (LQT8) is the consequence of CACNA1c gene mutation, manifested with LQTS, facial dysmorphia, syndactilia and neurocognitive insufficiency (14).

Specific triggers are associated with certain LQTS types. Physical exertion, especially swimming, and emotional stress contribute to LQT1symptoms, due to the lack of compensatory IKs increase in adrenergic stimulation (15). Possible explanations for the particular role of swimming include concomitant activation of sympathetic and parasympathetic autonomic system precipitating premature ventricular contractions, as well as QT interval prolongation due to cold-water face immersion, which both contribute to genetically caused IKs-deficiency (16). Most events in LQT2 and LQT3 are provoked by acute arousal/auditory stimulation or rest without arousal, respectively (17). Nevertheless, comorbidity of epilepsy with LQT2 due to KCNH2 expression in brain makes their differential diagnosis very important for therapeutic approach (18).

Diagnostic methods and criteria for LQTS

The diagnostic process begins with a thorough clinical and family history, focused on distinctive data about palpitations, repeated syncopes and their circumstances, „seizures" despite antiepileptic therapy, cases of SCD in the family or hereditary arrhythmias (7). Certain number of LQTS is revealed due to previous diagnosis of a family member.

Resting ECG with QT interval duration measurement remains crucial for the diagnosis. QT interval is usually corrected for heart rate using the Bazett's formula,

QTc=QT/√RR, expressed in milliseconds (ms), measured in leads II and V5/V6, with the longest value being used (18). Since there is no cut-off QTc value for LQTS, different authors give their references. According to the latest recommendations by the American College of Cardiology, the American Heart Association and the Heart Rhythm Society (AHA/ACCF/HRS) from 2009, prolonged QTc is considered ≥450ms for adult male and ≥460msfor adult female (19), while another study suggests borderline QTc≥470ms for adult female and ≥460ms for children under the age of 15 (table 2) (20). However, single ECG assessment could not be reliable, since 2.5% of healthy population may have a mildly prolonged QT interval and 25% of genotype-positive LQTS patients have normal QT interval, especially LQT1 (21). Besides, T wave morphology may help differentiate diverse types of LQTS (22). Usual ECG findings in fetal and neonatal LQTS are bradycardia and atrioventricular block (23).

Table 2. Suggested Bazett-corrected QTc values for diagnosing QT prolongation [ms] (19).

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

Exercise stress testing (EST) may help identifying abnormal QT prolongation during exercise or in the recovery, as well as the level of physical activity allowed to patients with LQTS. Pediatric population is characterized by more gradual deceleration in heart rate in recovery phase compared to the adults (24). The same study indicates that prolonged QT interval at peak exercise, in early (1-min) and late (7-min) recovery phase occurs in LQT1, while initial shortening and afterwards prolongation of QT interval in late recovery phase suggest LQT2 (24). QTc threshold value of ≥460ms in late recovery phase in children strongly refers to the LQTS and greater separation in the QTc intervals between the late and early recovery phases favors the diagnosis of LQT2 (24).

Additional diagnostic methods include serial ECG records, 24h ECG Holter and epinephrine test (8). Moreover, genetic analysis, which can confirm approximately 75% of phenotypically expressed LQTS, still remains to be widely established for clinical use (25). Negative genetic test does not exclude the diagnosis, whereas positive result may influence treatment decisions.

Considering the diagnostic adversity, *Schwartz et al* defined the scoring system (last revision in 2011), which assign points for ECG findings, clinical and family history (table 3) (26). Patients with Schwartz score ≥3.5, in the absence of secondary cause for QT prolongation, are di-

agnosed as LQTS (26). Although it would miss the latent LQTS patients, this system presents the basis of clinical LQTS diagnosing.

**Table 3.** Schwartz Score for LQTS diagnosis (updated in 2011) (25).

	Points
ECG findings	
QTc	
>480 ms	3
460–470 ms	2
450 (male) ms	1
4-min recovery QTc after exercise test ≥480 ms	1
Torsades de pointes	2
T-wave alternans	1
Notched T wave in 3 leads	1
Low heart rate for age	0.5
Clinical history	
Syncope	
With stress	2
Without stress	1
Congenital deafness	0.5
Family history	
Family members with definite LQTS	1
Unexplained sudden cardiac death <age 30 among immediate family members	0.5

QTc is calculated by Bazett's formula. Low heart rate for age means resting heart rate below the 2nd percentile for age.

Expert consensus published in 2013 defined criteria for the diagnosis of LQTS, which include: 1) Schwartz`s score ≥ 3.5 in the absence of a secondary cause for QT prolongation; 2) presence of pathogenic mutation in one of the LQTS genes; 3) QTc ≥ 500 ms in repeated 12- lead ECG in the absence of a secondary cause for QT prolongation; 4) QTc between 480 and 499 ms in repeated 12-lead ECGs in a patient with unexplained syncope, in the absence of a secondary cause for QT prolongation and pathogenic mutation (27).

Risk stratification

Risk assessment for a life-threatening cardiac event has the main role in the treatment planning. Higher risk of cardiac manifestations have boys under the age of 15 with LQT1, while for LQT2 and LQT3 in that age the risk is equal for both genders (28). Over 15 years old females are at higher risk in LQT1 and LQT2, and possible explanation for this sex distribution lies in sex hormones, inhibitory effect of estrogen on IKr and stimulatory effect of testosterone on IKs, with ensuing prolongation and shortening of APD, respectively (29). Furthermore, LQT3 patients have lower incidence of any type of cardiac event,
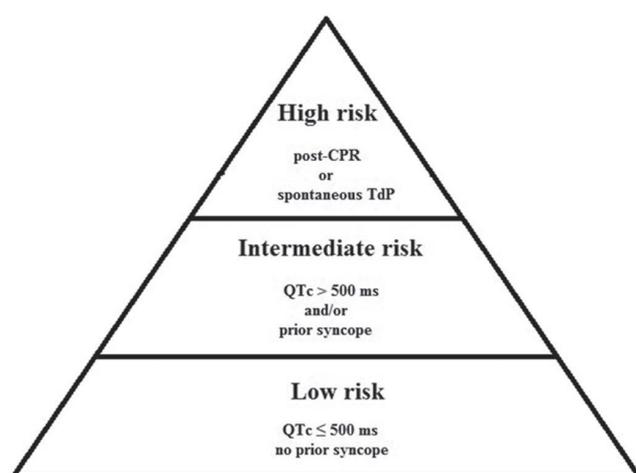
CPR -cardiopulmonary resuscitation.
TdP – Torsades de Pointes

Figure 2. Suggested risk stratification scheme for aborted cardiac arrest or sudden cardiac death in LQTS patients(30).

but followed with much higher lethality (3). Baseline QTc ≥ 500ms is an independent risk factor (19). The history of syncope and their frequency is one of the most powerful predictors of subsequent serious cardiac events in adolescents (30). Considering all the facts, LQTS risk groups for life-threatening cardiac event may be categorized as high, intermediate and low (figure 2) (31). However, since the phenotypic expression is time-dependent and age specific, it requires continuous risk assessment in affected patients.

Therapeutic consideration

As previously mentioned, treatment approach relays on risk assessment and it might be complex. The initial phase involves lifestyle modifications - avoiding competitive sport and extreme exertion, for LQT1 patients even non-competitive swimming (31); prompt electrolyte disorder corrections in diarrhea or vomiting; avoidance of medications known to prolong the QT interval (7). For patients with LQT2 is recommended preclusion of acoustic stimulation, such as alarm clock (17).

The first-line medical therapy involves β-blockers. They are presumed to act indirectly, through attenuation of cardiovascular adrenergic tone (7). The most effective have shown to be propranolol (2-4mg/kg/day) and nadolol (1-1.5 mg/kg/day) (32).Widely used in LQT1 and LQT2, lately has been indicated protective role of β–blockers in LQT3 (33). They should be administered to all intermediate and high risk patients and according to some authors even to low-risk individuals (8). Possible adjunctive therapy might be oral K+ supplementation, especially in LQT2 patients, whereas mexiletine and ranolazine effects for

LQT3 patients are still estimated in trials (34). However, in patients with repetitive cardiac events, a more invasive therapy should be considered.

Implantable cardioverterdefibrillator (ICD) is indicated for high-risk patients, post-cardiac arrest cases or those with numerous arrhythmic syncopal episodes who remain symptomatic despite β-blocker therapy, intoleration or contraindication for β-blockers, as well as JLN patients (27).

Left cervicothoracic sympathetic denervation (LCSD) is a surgical procedure of heart denervation by resection of left stellate ganglion and T2-T4 thoracic ganglia, introduced as treatment option even before medications (35). It is currently used for patients intolerant or irresponsive to β-blockers, patients in whom ICD implantation is unfeasible or who receive multiple ICD shocks (7).

Permanent pacemaker implantation is the last possible therapeutic option, combined with β-blocker therapy in patients with sinus bradycardia or pause-dependent TdP, but long-term follow-up studies still indicate an inappropriately high rate of SCD afterwards (36). Recent reports analyze focal radiofrequency ablation and gene-specific LQTS therapies as prospective therapeutic alternatives which appear to be promising.

Recommendation for sport participation for children with LQTS

It is proven in over 90% cases that cardiovascular diseases are the most important cause of sudden death in young athletes (37). Furthermore, incidence of SCD in young athletes is 2.5 times higher than the average rate of SCD (38). LQTS contributes with 2% in sudden cardiac death of young athletes in European population (38).

There are no official recommendations for physical activities in children with congenital LQTS, so they arise from the ones for adults. Cut-off values for prolonged QTc in athletes are >470ms for men and >480ms for women (39). The latest Bethesda recommendations for individuals with LQTS are: 1) for patients who experienced cardiac arrest or LQTS-precipitated syncopal episode are allowed only sports with low static and low dynamic intensity (class IA); 2) activities for asymptomatic patients with baseline QT prolongation should be restricted to class IA sport, except for genetically proven LQT3; 3) genotype-positive/phenotype-negative patient may be allowed to participate in competitive sports, except swimming for LQT1; 4) LQTS patients with an ICD/pacemaker should be restricted to class IA activities (table 4) (39). Considering such strict limitations, *Aziz et al* examined the consequences of neglecting the official recommendations and have not proven any cardiac event in LQTS children who

Table 4. Classification of sports (36).

	A. Low dynamic	B. Moderate dynamic	C. High dynamic
I Low static	Bowling	Fencing	Badminton
	Cricket	Table tennis	Race walking
	Golf	Tennis (doubles)	Running (marathon)
	Riflery	Volleyball	Cross-country skiing (classic)
		Baseball[a]/softball[a]	Squash[a]
		Field events (jumping)	Basketball[a]
		Figure skating[a]	Biathlon
II Moderate static	Auto racing[a,b]	Lacrosse[a]	Ice hockey[a]
	Diving[b]	Running (sprint)	Field hockey[a]
	Equestrian[a,b]		Rugby[a]
	Motorcycling[a,b]		Soccer[a]
	Gymnastics[a]		Cross-country skiing(skating)
	Karate/Judo[a]		Running (mid/long)
	Sailing		Swimming
	Archering		Tennis (single)
			Team handball[a]
			Boxing[a]
III High static	Bobsledding[a,b]	Body building[a]	Canoeing, Kayaking
	Field events (throwing)	Downhill skiing[a,b]	Cycling[a,b]
	Luge[a,b]	Wrestling[a]	Decathlon
	Rock climbing[a,b]	Snow boarding[a,b]	Rowing
	Waterskiing[a,b]		Speed skating
	Weight lifting[a]		Triathlon[a,b]
	Windsurfing[a,b]		

a - danger of bodily collision; b - increased risk if syncope occurs

were on beta-blocker therapy or with implanted ICD (40). These results suggest that the initial limitations might be too harsh, which implicates the need for further analysis.

Conclusion

Previous investigations of LQTS have broadened our knowledge, but have also raised many questions about the pathogenesis, diagnosis and treatment of these syndromes. Further genetic researches are expected to advance the understanding of genotype-phenotype correlation, provide novel insight into rare LQTS types and enable eventual genetically-guided personalized treatment in future. The relation between physical activity and LQTS manifestations is widely proven, since the first phase of LQTS treatment is avoiding competitive sport . Considering the differences among LQTS types, it is reasonable to presume more precise recommendations for physical activity of LQTS children.

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