doi: 10.20471/acc.2021.60.04.22

CONGENITAL LONG QT SYNDROME: A SYSTEMATIC REVIEW

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SUMMARY – Congenital long QT syndrome (LQTS) is a disorder of myocardial repolarization defined by a prolonged QT interval on electrocardiogram (ECG) that can cause ventricular arrhythmias and lead to sudden cardiac death. LQTS was first described in 1957 and since then its genetic etiology has been researched in many studies, but it is still not fully understood. Depending on the type of monogenic mutation, LQTS is currently divided into 17 subtypes, with LQT1, LQT2, and LQT3 being the most common forms. Based on the results of a prospective study, it is suggested that the real prevalence of congenital LQTS is around 1:2000. Clinical manifestations of congenital LQTS include LQTS-attributable syncope, aborted cardiac arrest, and sudden cardiac death. Many patients with congenital LQTS will remain asymptomatic for life. The initial diagnostic evaluation of congenital LQTS includes obtaining detailed personal and multi-generation family history, physical examination, series of 12-lead ECG recordings, and calculation of the LQTS diagnostic score, called Schwartz score. Patients are also advised to undertake 24-hour ambulatory monitoring, treadmill/cycle stress testing, and LQTS genetic testing for definitive confirmation of the diagnosis. Currently available treatment options include lifestyle modifications, medication therapy with emphasis on beta-blockers, device therapy and surgical therapy, with beta-blockers being the first-line treatment option, both in symptomatic and asymptomatic patients.

Key words: *Congenital long QT syndrome; Monogenic mutation; Syncope; Ventricular arrhythmia; Sudden cardiac death*

Introduction

The history of congenital long QT syndrome (LQTS) goes back to the year 1957 when Jervell and Lange-Nielsen first published an article describing four young siblings from nonconsanguineous parents, having a combination of congenital deafness and peculiar heart disease. Their electrocardiograms (ECG) revealed pronounced prolongation of the QT interval and they also suffered from syncopal episodes. Three of the deaf-mute children experienced sudden death at the ages of 4, 5, and 9 years, respectively[1]. Moreover, Levine and Woodworth[2] also described sudden deaths in children with congenital deafness. On the other hand, Romano *et al.*[3] and Ward[4] have reported additional families with prolonged QT intervals and sudden deaths, but without deafness. The importance of their work was soon acknowledged, thus since 1975 a unifying name 'long QT syndrome' differentiates two types, a rare autosomal recessive form with concomitant congenital deafness, referred to as the Jervell-Lange-Nielsen syndrome, and a more frequent autosomal dominant form without concomitant congenital deafness, referred to as the Romano-Ward syndrome[5].

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Received January 29, 2021, accepted September 20, 2021

Pathophysiology and Genetics

The QT interval represents the time from the initiation of ventricular depolarization to the end of ventricular repolarization. In the majority of congenital LQTS patients, mutations in the genes that encode cardiac ion channels result in prolongation of the action potential, therefore congenital LQTS is considered a cardiac channelopathy. Depending on the type of monogenic mutation, LQTS is currently divided into 17 subtypes, with LQT1, LQT2, and LQT3 being the most common forms making up to 75% of all patients with LQTS[6,7]. Mutations in minor LQTS genes account for 5% of congenital LQTS, whereas about 20% of all patients will have established clinical diagnosis of LQTS but without identifiable gene mutation[8,9]. A recently published article questions the causality of all the currently known LQTS gene mutations in inducing the disease, considering dramatic changes in recent understanding of human genetic variation. In the mentioned study, 3 gene curation teams independently scored the level of evidence for 17 genes reported to cause LQTS. Only 3 genes (KCNQ1, KCNH2, and SCN5A) were curated as definitive genes for typical LQTS. These three genes are the ones that make the major forms of LQTS (LQT1, LQT2, LQT3, respectively). Four genes (CALM1, CALM2, CALM3, and TRDN) were found to have strong or definitive evidence for causing LQTS but with atypical features. One gene (CACNA1C) showed a moderate level of evidence for causing LQTS[7]. Mutations in the CALM1-3 gene are now known as calmodulinopathy[10], while mutation in the TRDN gene is currently referred to as Triadin Knockout Syndrome. Both of these novel clinical entities now have their own International Registry for patient enrollment[11,12]. Mutation in CACNA1c, voltage-gated calcium channel gene, is part of the complex Timothy syndrome, a rare variant of congenital LQTS, also known as LQT8. It is a highly malignant form of LQTS that often presents with 2:1 functional atrioventricular block and multi-system disorder[5].

The LQT1 and LQT2 include loss-of-function mutations (KCNQ1 and KCNH2 genes, respectively) in the potassium channels, which cause decreasing activity of the slow delayed rectifier current (IKs) and rapid delayed rectifier current (IKr) (phase 3 of the action potential), respectively. LQT3 includes gain-of-function mutation (SCN5A gene) in the sodium channel (phase 0 of an action potential) that causes persistent sodium influx that extends through the plateau phase. A loss of IKs or IKr function, or gain of INa function, in most cases, predisposes ventricular myocytes to early afterdepolarizations (EADs). When regions of the myocardium develop EADs synchronously, it can trigger lethal ventricular arrhythmias, including *torsades de pointes*[13].

Epidemiology

For a long period of time, congenital LQTS was considered a rare syndrome with an estimated prevalence anywhere between 1/5,000 and 1/20,000. However, there were no actual data that could support these assumptions. In 2009, Schwartz *et al.*[14] published the first prospective study, which included 44,596 infants. The newborns underwent ECG recordings together with additional genetic analysis of 7 LQTS genes in those with established prolonged QTc >470 ms. The results demonstrated a prevalence of congenital LQTS of at least 1:2,534 apparently healthy live births. Results of the study showed that, unlike other channelopathies, congenital LQTS is more unrecognized than rare. The prevalence is suggested to be even higher because only infants with a QTc >470 ms were molecularly screened, thus it has been suggested that the real prevalence of congenital LQTS is around 1:2000. A long time ago, it was postulated by Schwartz *et al.*[15,16] that the prevalence of LQTS when including silent carriers (genotype positive, phenotype negative individuals) was actually much higher. Data from the population-based Exome Sequencing Project, published in 2013, estimated the prevalence of the 'pathogenic' LQTS genotype to be 1:80, which is in great discordance with the prevalence of the expressed QTc clinical phenotype of 1:2000. Even when taking incomplete penetrance and variable expressivity of LQTS genes into account, this discrepancy is still not fully understood[17].

Clinical Manifestations

Clinical manifestations of congenital LQTS are very variable, with the risk of malignant outcomes laying greatly upon the difference of molecular genetics in each type[5]. Clinical manifestations of congenital

Table 1. Schwartz score

ECG findings (in the absence of medications or disorders known to affect these features):
• QTc (= QT/√RR, interpret with caution with tachycardia since QTc overcorrects at fast heart rates)
- ≥480 milliseconds: 3 points
- 460 to 479 milliseconds: 2 points
- 450 to 459 milliseconds (in males): 1 point
• QTc at fourth minute of recovery from exercise stress test ≥480 milliseconds: 1 point[27]
• *Torsades de pointes** (in the absence of drugs known to prolong QT): 2 points
• T wave alternans: 1 point
• Notched T wave in three leads: 1 point
• Resting heart rate below second percentile for age (restricted to children): 0.5 point
• **Clinical findings:**
• Syncope* (*points for documented *torsades* and syncope are mutually exclusive)
- With stress: 2 points
- Without stress: 1 point
• **Family history** (the same family member cannot be counted in both of these criteria):
• Family members with LQTS: 1 point
• Unexplained SCD in immediate family members <30 years of age: 0.5 point

SCD = sudden cardiac death; low probability ≤1 point; intermediate probability 1.5 to 3 points; high probability ≥3.5 points

LQTS include LQTS-attributable syncope or seizures, aborted cardiac arrest, and sudden cardiac death. Many patients with congenital LQTS will remain asymptomatic throughout their life. Based on data from the Mayo Clinic, only 27% of the patients were symptomatic prior to their first clinical evaluation. The median age at the time when the first symptom occurred was 12 years[18]. LQTS-attributable syncope is arrhythmogenic in its nature with typically polymorphic ventricular tachycardia (VT) in its origin. Syncopal episodes may be accompanied by tonic-clonic movements and thus misdiagnosed as epilepsy[19]. The majority of arrhythmias in patients with congenital LQTS are ventricular tachyarrhythmias, with polymorphic VT being the classic arrhythmia associated with the disease. The minority of patients with congenital LQTS can present with somewhat atypical features such as atrioventricular (AV) block, atrial arrhythmias, and not so rare accompanying sinus bradycardia[20]. Among the associated findings in patients with LQTS, the most common ones are hearing loss and congenital heart disease[19]. Based on the data from the Mayo Clinic published by Rohatgi *et al.*, 1 of 4 previously symptomatic patients experience at least 1 non-lethal LQTS-trigger red cardiac event. The same study showed the mortality of congenital LQTS with appropriate medical therapy to be 0.3% nowadays[18].

Diagnosis

The initial diagnostic evaluation of congenital LQTS includes obtaining detailed personal and multigeneration family history, physical examination, series of 12-lead ECG recordings, and calculation of the LQTS diagnostic score, called Schwartz score (Table 1). During the initial diagnostic assessment, secondary causes of congenital LQTS, such as acquired LQTS, should be excluded. When there is a high probability of establishing the diagnosis of congenital LQTS, patients are advised to undertake 24-hour ambulatory monitoring, treadmill/cycle stress testing[21,22], and LQTS genetic testing for definitive confirmation of the diagnosis.

Personal history should be evaluated for the abovementioned clinical manifestations of the disease, such as syncope, seizures and sudden cardiac arrest.

Family history should be questioned for premature sudden deaths, unexplained accidents, unexplained drownings, or seizure disorders, while, as previously mentioned, syncope episodes with seizure characteristics are commonly misdiagnosed as epilepsy in LQTS families.

In the majority of patients with LQTS, physical examination reveals no particularity, but some patients may have concomitant abnormalities that appear as part of the LQTS syndromes. Hence, congenital deafness may indicate the Jervell-Lange-Nielsen syndrome, skeletal abnormalities, such as short stature and scoliosis can present as part of the Andersen-Tawil syndrome, whereas congenital heart diseases, cognitive and behavioral problems, musculoskeletal diseases, and immune dysfunction usually indicates Timothy syndrome.

Every patient should have 12-lead ECGs performed with the calculated value of the corrected QT interval (QTc). QTc is the most useful diagnostic and prognostic parameter for LQTS and is still mostly calculated by the Bazett's formula, despite some criticism. QTc should be measured in leads II and V5 on serial ECGs. The average QTc values in healthy adults are 420±20 milliseconds with 99th percentile values being 460 milliseconds (prepuberty), 470 milliseconds (postpubertal males), and 480 milliseconds (postpubertal females). In an asymptomatic patient with no family history, pre-test probability favors outliner over a LQTS until the QTc is over 500 ms. Apart from QTc value, many patients with congenital LQTS present with some bizarre pattern in their ECGs. The most common finding is difference in the T wave morphology with the T waves often being biphasic or notched. T wave pattern in patients with congenital LQTS also includes T wave alternans, which identify patients at a particularly high risk. T wave alternans consist of beat-to-beat alternation of the T wave, in polarity or amplitude, and in that term it is a marker of great electrical instability of the heart and may precede *torsades de pointes*. These somewhat additional findings are insensitive, so the absence of an abnormal T wave morphology does not exclude patients from having congenital LQTS[5].

Exercise testing

An exercise ECG stress test is a valuable part of the initial diagnostic evaluation, while it is known that arrhythmias in patients with LQTS are frequently triggered by external events, especially exercise. However, an exercise test is not only used to trigger arrhythmias but it can also detect changes in the T wave morphology and presence of abnormal QT response during the recovery phase. This phenomenon is particularly observed in patients with LQT1 since their genetic impairment lies in the function of the Kv7.1 outward-rectifying potassium channels. The impaired function of Kv7.1 channels contributes to shortening of the action potential during activation of the sympathetic nervous system, which in great measure takes place during exercise. For this reason, the QT interval in patients with LQT1 may be unable to shorten or may even lengthen with activity and at higher heart rates. Furthermore, notable prolongation of QT may also be observed during the recovery phase after exercise. These characteristics coincide with the published data that 62% of cardiac events in LQT1 occur during exercise[21]. The findings in LQT2 are a bit different and consider the possibility of the mentioned subtype if the QTc at five minutes of recovery is ≥470 milliseconds, and is 40 to 50 milliseconds greater than the QTc at one minute of recovery. In patients with LQT3, findings associated with flawed shortening of QT interval during exercise and recovery are not found.

Schwartz score

In the literature on congenital LQTS, since the early discoveries of the syndrome, the name of Doctor Peter Schwartz is most frequently encountered, so it is not surprising that the diagnostic criteria have been named after him. In 1985, Schwartz[23] suggested the first-ever diagnostic criteria for congenital LQTS that still serve as the best criteria for clinicians. Revisions of criteria were published in 1993[24], 2006[25], and 2011[26].

When a patient satisfies a high probability Schwartz score (i.e., ≥3.5 points), the likelihood of a positive LQTS genetic test is approximately 80 percent. Intermediate probability Schwartz score warrants further pursuit of the possibility of congenital LQTS (i.e., genetic testing of the patient and ECG testing of his/her relatives). The likelihood of LQTS is approximately a 5 to 20 percent chance, far higher than the 1 in 2000 background rate for this disease. If the Schwartz score is low (<1 point), genetic testing should not be pursued and these patients should be referred to as normal.

Ambulatory ECG monitoring

As mentioned earlier, patients with LQTS cardiac events are often triggered by external events such as stress, noise, exercise, etc. However, even without significant clinical manifestations, daily patient activity, or even time of the day can result in different patterns and features in the ECG. In that term, Holter monitoring can be a useful tool for detecting ECG characteristics such as intermittent QT prolongation, bradyarrhythmia, macroscopic T wave alternans, and T wave notching that can vary during the day[27-29].

Genetic testing

In modern medicine, which aspires to become individualized and personalized in its treatment plan for each patient, genetic testing should be viewed as a standard of care in the diagnostic and prognostic evaluation of LQTS. Regardless of that, genetic testing is still somewhat of a rarity in today's clinical practice, even when facing a disease with the causality in genetic modifications. Genetic analysis is helpful in many ways because it may establish the diagnosis when it is uncertain and identify affected family members. Furthermore, perhaps the most valuable benefit of genetic testing lies in its prognostic and therapeutic significance.

By determining the causative mutation, the physician can design a more individualized treatment program and establish a more precise prognosis of the disease because some highly malignant forms are connected with certain mutations and the severity of the disease greatly depends on the LQTS subtype. It is important to emphasize that congenital LQTS still has a number of unanswered questions regarding its genetic genesis, and according to today's classification, it is a complex and heterogeneous condition where a negative test does not exclude the disease.

Current guidelines[30] recommend genetic testing in the following cases:

(a) high clinical suspicion of congenital LQTS based on history, family history, ECG findings, and results of any additional testing such as a high Schwartz score ≥3.5 (class I recommendation);

(b) intermediate clinical suspicion of congenital LQTS based on history, family history, ECG findings, and results of any additional testing such as an intermediate Schwartz score of 1.5 to 3 (class II recommendation);

(c) asymptomatic patients without a family history of congenital LQTS but who have serial ECGs with QTc ≥480 milliseconds before puberty or ≥500 milliseconds post-puberty (class I recommendation);

(d) asymptomatic patients without a family history of congenital LQTS but who have serial ECGs with QTc ≥460 milliseconds before puberty or ≥480 milliseconds post-puberty (class II recommendation); and

(e) cascade/variant-specific testing of all appropriate relatives when the disease-causative variant has been identified in the proband (class I recommendation).

Treatment

Currently, there is no causal treatment in the management of LQTS. Available treatment options today include lifestyle modifications, medication therapy with emphasis on beta-blockers, device therapy, and surgical therapy. Beta-blockers as the first-line therapy option address the most common trigger for the main cardiac events such as a sudden increase in sympathetic activity, which is mainly predominated by the left cardiac sympathetic nerves[31].

While antiadrenergic therapies have been proven to provide the greatest degree of protection, not all cardiac events in LQTS happen because of sympathetic activation[32]. As discussed earlier, triggering effects are largely gene dependent, with some patients having syncope episodes while being asleep or resting, or when they are suddenly aroused from these states. Furthermore, in some patients the arrhythmias are pause dependent[15].

Beta-blocker therapy

As mentioned before, beta-blockers currently are first-line therapy in LQTS patients. Studies have shown that implementing beta-blockers as a treatment dramatically decreases cardiac event rates from 0.97 to 0.31 events *per* patient *per* year[33]. According to current guidelines, beta-blockers are recommended for all symptomatic patients with congenital LQTS if there are no contraindications for their use[31].

Due to the fact that it is difficult to assess the risk of experiencing LQTS-associated events, beta-blocker therapy is also recommended for the majority of asymptomatic LQTS patients.

However, in asymptomatic patients with a QTc <470 milliseconds, therapy may not always be required.

Furthermore, sometimes the risk-benefit calculation in asymptomatic patients will favor a non-therapy approach, especially in older patients with no excessive

QTc prolongation and genetically lower-risk LQTS subtype[34].

Beta-blockers have been proven to be extremely effective in LQT1 patients, presumably because of the high sympathetic sensitivity observed in this disorder. Data from two large studies[35,36] indicate that mortality is around 0.5% and sudden death combined with cardiac arrest reaches 1% in LQT1 patients when using beta-blocker therapy. Although the greatest benefit from therapy is observed in LQT1 patients, beta-blocker therapy is also very effective in both LQT2 and LQT3 patients. In comparison with LQT1, LQT2 patients have more life-threatening events despite the same beta-blocker treatment, but most of these are resuscitated cardiac arrest (6%-7%)[35]. Patients with LQT3, despite beta-blocker therapy, experience major cardiac events more frequently (10%-15%)[15,35], and a certain number of these patients will require additional therapies. What is more, many patients with Jervell-Lange-Nielsen syndrome are not adequately protected by beta-blockers[36,37].

There are limited data comparing the efficiency of different beta-blockers in the treatment of congenital LQTS. In the study by Abu-Zeitone *et al.*[38], results showed the risk reduction in LQT1 for first cardiac events to be similar among the atenolol, metoprolol, propranolol, and nadolol, but in LQT2, nadolol was found to be the only beta-blocker that provided significant risk reduction for cardiac events.

Furthermore, there were differences in the probability of recurrent events in patients with LQTS, with propranolol therapy being least effective. Therefore, there is a consensus among experts that nadolol should be the preferred first-line drug therapy in LQTS. Nadolol is used at a dose of 1-1.5 mg/kg/day (once a day for patients older than 12 years; divided twice a day for younger patients). Although there is no conclusive recommendation for the next best option, the Heart Rhythm Society (HRS) survey and the largest LQTS centers have used propranolol in this scenario[39].

A study by Chockalingam *et al.*[40] showed equal efficiency comparing propranolol and nadolol, whereas symptomatic patients using metoprolol showed a significantly higher risk of major cardiac events. Thus, the recommendation from the study is not to use metoprolol in symptomatic LQT1 and LQT2 patients. On the other hand, propranolol is mostly used at a dose of 2 to 3 mg/kg *per* day. Sometimes, the dosage is increased to 4 mg/kg, and in the rare more malignant cases, higher doses are equally justified[41]. It was observed[36,37] that so-called failures of beta-blocker therapy are mostly due to incomplete compliance. Thus, it is of great importance to explain to patients the value of therapy and thus ensure acceptable compliance. When beta-blocker therapy is proven to be inadequate, in terms of the onset of breakthrough cardiac events while on therapy or in case of beta-blocker intolerance, individualized patient therapy should be evaluated. Based on the assessed risk from the disease and the potential adverse effects of various treatments, treatment options may include one or more of the following:

- other medications (such as mexiletine);
- left cardiac sympathetic denervation (LCSD); and
- placement of an implantable cardioverter-defibrillator (ICD).

Mexiletine therapy

The effect of mexiletine, which belongs to the class IB group of antiarrhythmics, is mutation-specific in patients with LQT3[42]. Thus, it is recommended to test its effectiveness in all LQT3 patients under continuous ECG monitoring by the acute oral drug test technique. It was observed that mexiletine in LQT3 patients had both QT-attenuating, as well as significant protective effects. Combination therapy with propranolol and mexiletine is increasingly used today in patients with LQT3. However, in high-risk LQT2 patients, drug therapy with a beta-blocker and mexiletine may be considered as well[43]. Dosing of mexiletine is usually 4 to 6 mg/kg/dose administered approximately every eight hours.

Left cardiac sympathetic denervation

Left cardiac sympathetic denervation involves removal of the first four thoracic ganglia, which results in interrupted release of the major source of norepinephrine in the heart[44]. There is no reinnervation, while denervation is preganglionic. The procedure is considered not to be complicated and is performed by the extrapleural approach with a small incision in the left subclavicular region.

A study published by Schwartz *et al.* in 2004[45] included 147 LQTS patients who underwent sympathectomy during the past 35 years. They represented a group at high risk, while 99% of them were symptomatic with an extremely long mean QTc (563±65 ms);

48% of them had a previous cardiac arrest, and 75% had recurrent syncope despite full-dose beta-blockers. During a mean follow-up of 8 years, a 91% reduction in cardiac events was observed. Based on these encouraging results, current recommendations suggest that whenever syncopal episodes recur despite full-dose beta-blocking therapy, LCSD should be considered and implemented if possible.

Implantable cardioverter-defibrillator

Implantable cardioverter-defibrillators take an important part of congenital LQTS management algorithm, especially among patients who presented with sudden cardiac arrest or those who have recurrent major cardiac events[46-49]. However, in 31% of patients, within five years of ICD placement, complications such as infection, lead fracture and dislodgement, inappropriate discharges, and psychiatric consequences occur[50]. For these reasons, ICDs are considered only in a certain number of patients with congenital LQTS. In fact, based on experiences from LQT major centers, 90% or more patients with LQTS do not need and should not receive an ICD just because they have been diagnosed with LQTS, even so in LQT3 where the highest ICD implant rates have been noted[50]. The overall consensus is that immediate implanting an ICD is reserved for cases in which cardiac arrest has been documented, with or without concomitant therapy. The ICD should also be implanted in those with syncopal episodes despite taking a full dose beta-blocker and having an LCSD, as well as in those in whom LCSD has been discarded as an option for whatever reason. Schwartz *et al.*[50] suggest a prophylactic ICD in asymptomatic LQT2 and LQT3 patients whose resting QTc is >550 milliseconds. In LQT2 women after puberty whose resting QTc >500 milliseconds, prophylactic ICD is considered reasonable.

For patients with Lange-Nielsen syndrome or Timothy syndrome who appear to be incompletely protected by antiadrenergic treatment alone, a possibility of triple therapy including beta-blocker, LCSD, and ICD should be considered.

Lifestyle modifications, physical activity and LQTS

Apart from the treatment options discussed above, all patients with congenital LQTS should be advised simple QT preventive measures and encouraged to implement them whenever possible. These include avoidance of medications with QT-prolonging potential (www.crediblemeds.org), replacing electrolytes during vomiting and diarrheal illnesses, and lowering fever because all those mentioned can aggravate QT prolongation. One of the important questions when considering lifestyle modifications is physical activity recommendation in LQTS patients. Current recommendations[30] allow patients with LQTS to continue to be recreationally active, especially those with LQT2 and LQT3, but naturally, after establishing the right diagnosis and implementing the initial treatment program. Professional athletes with LQTS should be evaluated by an LQTS specialist if they desire to remain in competitive sports. Importantly, there are legal acts in some countries that supersede professional society guidelines regarding return-to-play issues.

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Sažetak

SINDROM DUGOG QT INTERVALA: SUSTAVNI PREGLED

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Sindrom dugog QT intervala (LQTS) nasljedni je poremećaj repolarizacije miokarda obilježen produženim QT intervalom u elektrokardiogramu (EKG) koji može uzrokovati maligne ventrikulske aritmije i iznenadnu srčanu smrt. LQTS prvi je puta opisan 1957. godine, a iako je njegova genetska podloga mnogo puta istraživana, etiologija još uvijek nije u potpunosti razjašnjena. Ovisno o tipu monogenske mutacije LQTS se može podijeliti u 17 podtipova od kojih su najčešći LQTS1, LQTS2 i LQTS3. Procjenjuje se da učestalost kongenitalnog LQTS iznosi oko 1:2000. Klinička slika LQTS može uključivati sinkopu, srčani zastoj i iznenadnu srčanu smrt. Velik dio bolesnika s kongenitalnim LQTS ostaje asimptomatski tijekom cijeloga života. Dijagnostičku obradu kongenitalnog LQTS čini detaljna osobna i obiteljska anamneza, fizikalni pregled, serijsko praćenje 12-kanalnog EKG-a te izračun Schwartzovih dijagnostičkih kriterija. Također treba isključiti moguće sekundarne uzroke stečenog LQTS. Uz to, bolesnicima se savjetuje učiniti 24-satni holter EKG i test opterećenja, a za konačnu potvrdu dijagnoze genetsko testiranje. Terapijske mogućnosti uključuju promjene životnih navika, medikamentnu terapiju s naglaskom na beta-blokatore, implantaciju kardioverter defibrilatora i kirurško liječenje, pri čemu su beta-blokatori prvi izbor terapije i kod simptomatskih i asimptomatskih bolesnika.

Ključne riječi: *Kongenitalni sindrom dugog QT intervala; Monogenska mutacija; Sinkopa; Ventrikulska aritmija; Iznenadna srčana smrt*