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Genetic Disease Modifying Future Career: A Case Report of Long QT Syndrome

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Abstract

Long QT syndrome (LQTS) is a rare congenital and inherited or acquired heart condition in which delayed repolarization of the heart following a heartbeat increases the risk of episodes of *torsades de pointes*. These episodes may lead to fainting and sudden death due to ventricular fibrillation. Long QT syndrome is a channelopathy, characterized by the disorder of ion channels, which results in a prolongation of QT interval and ventricular arrhythmias. Clinical manifestation of long QT syndrome varies from asymptomatic to life threatening arrhythmias. The first sign of the disease may be sudden cardiac death. Episodes may be provoked by various stimuli, depending on the subtype of the condition. Therefore, once the syndrome is diagnosed, prevention of adverse events should be started that could often change the lifestyle and sometimes future career.

We present a case of an asymptomatic 15-year-old athlete girl, in whom long QT syndrome type 1 was diagnosed leading to termination of her professional sport career. Prolongation of QT interval was identified during routine health screening. The intermediate probability of long QT syndrome was calculated according to Schwartz and Crotti criteria, therefore genetic testing was performed showing pathogenic mutation of *KCNQ1* gene. After the genetic confirmation of the disease, patient's medical examination was reviewed showing QTc interval prolongation on recovery phase during exercise stress test.

A scrutiny examination of athlete's electrocardiograms is needed. Automatic calculation of QTc interval can be imprecise and manual recalculation is necessary. Accurate evaluation of LQTS ECG criteria helps to determine the probability of genetic syndrome, indications for genetic testing, lifestyle and treatment recommendations.

Keywords: Long QT syndrome; Torsades de pointes; Sudden cardiac death

Abbreviations: LQTS: Long QT Syndrome; ECG: Electrocardiogram

Introduction

Long QT syndrome (LQTS) is a genetic disorder characterized by a prolongation of QT interval (prolonged ventricular repolarization) and it is complicated by syncope and sudden death [1]. Estimated prevalence of long QT syndrome is approximately 1 in 2000 individuals (0.05%) [2,3] and 0.4% among athletes [4]. To date 15 genes associated with LQTS have been identified [5]. Although some of the patients have no complaints, the first manifestation of the disease may be sudden cardiac death [2]. Therefore, we present a case of an asymptomatic athlete girl, who had to change her future career plans because of the dangerous but sometimes overlooked hereditary disorder.

Case Presentation

The 15-year-old girl was a professional athlete in biathlon for 7 years. In 2013, routine health screening was performed at Sports Medicine Center. Electrocardiogram (ECG) at rest showed sinus rhythm and prolongation of QT interval up to 520 ms. The patient had no complaints, episodes of fainting or weakness were absent. The family history revealed that her father died suddenly at the age of 57, the cause of his death remained unknown. The girl was referred to the Vilnius University Hospital Santariskiu klinikos for the further examination and treatment.

Cardiological examination revealed that the patient's heart rate was 57 beats/minute, blood pressure 100/70 mmHg. Blood electrolytes (potassium, sodium, magnesium, calcium) were normal. Repeated ECG showed sinus rhythm and prolongation of QTc interval up to 513 ms (Figure 1). Exercise stress test was performed, arrhythmias were not registered, hemodynamic response to stress was hypertensive and respiratory failure was not revealed. However, QTc interval remained prolonged, during first minute of exercise QTc was 473 ms. In up to 90% of 24 hours Holter ECG monitoring, prolongation of QT and QTc interval was registered (calculated according to heart rhythm). Transthoracic echocardiography did not reveal any pathological changes.

Genetic counselling assessment was performed for the patient. Additional (syndromic) features of long QT syndrome were not observed. Analysis of genealogy showed that patient's father died at the age of 57 years and her cousin reportedly had epilepsy (Figure 2). Intermediate probability of LQTS (3 points) was calculated using Scoring System for Clinical Diagnosis of Long QT Syndrome (adapted from Schwartz and Crotti) [6,7]. In order to confirm the diagnosis and to identify the type of the syndrome, which is important for the lifestyle; it was decided to perform genetic testing. Furthermore, the patient had a significant opposition to the diagnosis, did not want to end a sport career. Genetic confirmation was as important to her brother, who was also a professional athlete and did not have prolongation of QTc interval on ECG. Genetic testing of 13 genes associated with LQTS (*KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, *CAV3*, *SCN4B*, *AKAP9*, *SNTA1*, *KCNJ5*, *ANK2*, *CACNA1C*, *KCNJ2*) was performed and heterozygous pathogenic *KCNQ1* gene missense type variant c.568C>T (p.Ala190Trp) was identified. This variant has been detected previously

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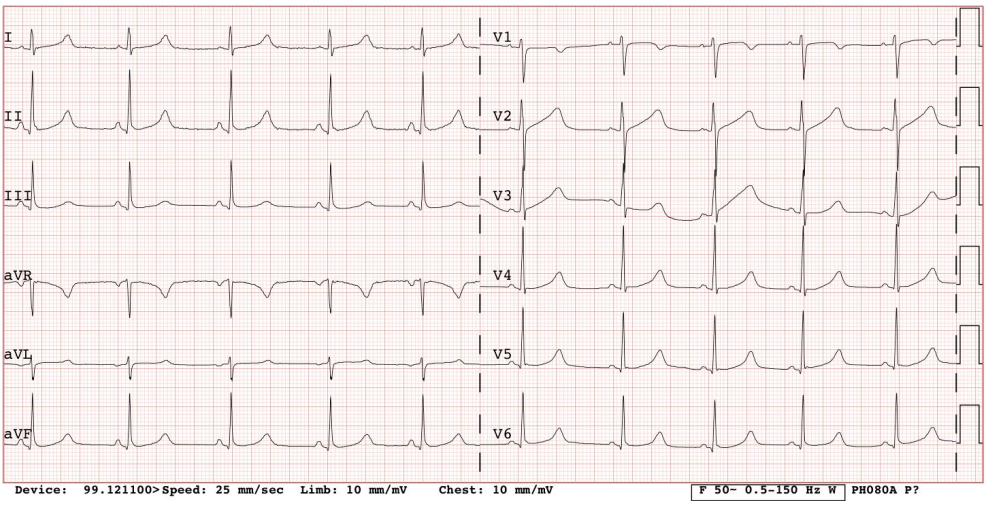

Figure 1: Repeated ECG showing prolongation of QTc interval 513 ms.

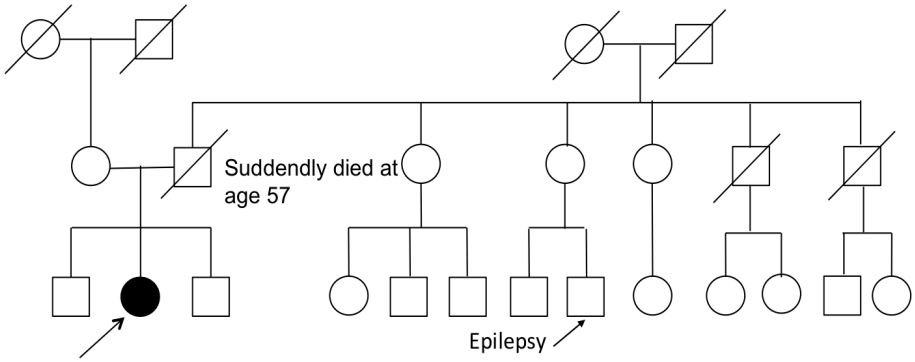

Figure 2: Genealogical family tree of the patient. Her father died suddenly at age of 57.

multiple times in LQTS patients and is evaluated as pathogenic in The human Gene Mutation Database [8] and likely pathogenic in ClinVar database [9]. Therefore, the diagnosis of LQTS type 1 was established.

After genetically confirmed diagnosis, we looked through patient's medical examination once more and manually calculated QTc interval during exercise stress test. During the 4th minute of recovery QTc remained long and was 518 ms. This finding adds 1 point to risk score according to Schwartz by reason of QTc interval ≥ 480 ms on fourth minute recovery after exercise stress test. Therefore, long QT syndrome risk score increases to 4 points (high risk).

The patient was advised to avoid any sports and propranolol was prescribed. Genetic testing of familial *KCNQ1* pathogenic variant was recommended for the proband's family. It was also recommended not to take QT interval prolonging medications. The patient was given the information about QT interval prolonging medications on the Internet (www.crediblemeds.org).

Discussion

LQTS type 1 is induced by pathogenic variant of *KCNQ1* gene located on chromosome 11. Genetic change interrupts the structure of coding protein consequently impairing its function. Slow outward delayed potassium current has been observed in patients with genetically confirmed long QT syndrome [10]. Prolongation of QT interval is not constant and the duration of the QT interval may vary [11]. Clinical presentation can also vary from asymptomatic one to sudden death. This girl had asymptomatic presentation of LQTS. Unfortunately, the absence of symptoms does not reduce the risk of life threatening arrhythmias. LQTS may remain completely clinically silent until the first serious manifestation. The patients with long QT syndrome may develop torsade de pointes ventricular tachycardia. This arrhythmia is responsible for cardiac events such as syncope, cardiac arrest, sudden death [11].

Differential diagnosis of syncope is important. Long QT syndrome could easily be misdiagnosed as epilepsy, as clinical picture of seizures could be caused by cerebral hypoperfusion during ventricular arrhythmia [3,5,12]. It is known that epilepsy is diagnosed for the patient's cousin. The clinical picture of seizures has not been elucidated yet; therefore, the patient requires more thorough examination, in order to exclude LQTS or other factors causing syncope. According to Johnson et al. (2009) study, a seizure phenotype was more common in type 2 of long QT syndrome than in type 1 or type 3, though differential diagnosis is important for proper treatment [13].

Commonly, long QT syndrome is being diagnosed on the basis

of duration of QTc ≥ 480 ms in repeated 12-lead ECGs, risk score >3 (based on Scoring System for Clinical Diagnosis of Long QT Syndrome of Schwartz & Crotti) and confirmed pathogenic variant of long QT syndrome genes [6]. Scoring System for Clinical Diagnosis of Long QT Syndrome was developed in 1985 and it was revised for several times [7,14-16]. According to European Society of Cardiology Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death [6], clinical diagnosis of LQTS was reasonable. Originally, we calculated intermediate probability of LQTS in our patient, and it was decided to perform genetic testing because of remaining high suspicion of inherited LQTS (unclear genealogy data, including father's death and cousin's seizures), despite the analysis of genealogy data did not fit Schwartz and Crotti criteria. Moreover, we considered that the results of genetic testing were very important for patient's career and risk estimation for family members (patient's brother is professional athlete). Furthermore, as the patient was a female of childbearing potential, the results would be important for life style requirements after labor and during nursing (in event of type 2 LQT syndrome, when there are special requirements for mother's nutrition and protection from noise-caused stress). Furthermore, it was taken into account, that transmission of LQTS gene to the children was possible. The results of genetic testing not only confirmed the clinical diagnosis of LQTS but enabled us to identify the type of this disease. It is important to distinguish the types of LQTS, in order to avoid main triggers of sudden cardiac death, including exercise, swimming or unexpected loud noise [15] and choose an appropriate treatment. In LQTS type 1, arrhythmias and sudden cardiac death are associated with exercise, especially swimming [11,17]. Therefore, this patient was at risk of life-threatening arrhythmias caused by physical activity.

In our case, the patient had high probability of inherited long QT syndrome as it was reviewed after the syndrome confirmation by genetic testing. ECG parameters were calculated automatically during exercise stress test. Therefore, prolongation of QTc interval during fourth minute of recovery was not registered. Only after manual calculation of ECG parameters prolongation of QTc ≥ 480 ms on fourth minute of recovery after exercise stress test was observed. Commonly QTc interval is calculated automatically in 12-lead ECG. However, this method could be imprecise. Computer-derived QTc measuring accuracy is 80–90%, therefore automatically calculated QTc interval must be confirmed manually [3]. An individualized corrected QT interval measured from 24-hour Holter data more accurately predicts carriers of a pathogenic LQTS mutation than QT corrected using the Bazett formula and calculated from a 12-lead ECG [18]. A detailed examination of ECG is required, especially after exercise stress test, as prolongation of QTc interval recorded in ECG can be the only one diagnostic feature suggestive to LQTS.

There are many debates if the patient is eligible to continue professional sport career. According to Johnson et al. (2013) study, a low rate of cardiac events and no deaths were observed among athletes with long QT syndrome who decided to remain in competitive sports [19]. Despite the fact that for this patient arrhythmias and symptoms had not occurred during training and competitions, further sport activity was not recommended, and pharmacologic treatment was started [20]. Beta blockers are more likely to be beneficial in case of LQTS1 compared with LQTS2 or LQTS3 [21]. Based on the current evidence, of the effectiveness of beta blockers in carriers of a *KCNQ1* pathogenic variant, pharmacologic treatment should be started even if patient is otherwise asymptomatic. The risk of death may be almost eliminated for patients who take beta blockers regularly and avoid QT-prolonging drugs [20]. Beta blocker that the patient should use is considered as doping in professional sport and it suspends her professional career [22]. In some cases (e.g. previous cardiac arrest episode, contraindicated or ineffective beta blockers) implantable cardioverter defibrillators should be considered [17].

Conclusion

A scrutiny examination of athlete's electrocardiograms is needed. Automatic calculation of QTc interval can be imprecise and manual recalculation is necessary.

Accurate evaluation of LQTS ECG criteria helps to determine the probability of genetic syndrome, indications for genetic testing, lifestyle and treatment recommendations.

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