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Prolonged *QT* interval on electrocardiogram and fainting — is there always a relationship?

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Abstract

Using a clinical example, the article draws the attention of doctors to the problem of the prolonged *QT* interval ("long *QT*") and the related problem of fainting (syncope). Syncope is a component of long *QT* syndrome, and syncope is a precursor of sudden cardiac death. However, syncope in a patient with long *QT* syndrome may have pathogenesis that is completely unrelated to abnormalities of cardiac ion channels. In other words, such a patient may have a second disease as a syntropy relates to prolonged *QT* interval, to an extent mimicking long *QT* syndrome. The presented medical history of a 33-year-old patient S. shows the complexity of differential diagnosis of the causes of syncope. The crucial part in the diagnosis, in addition to the clinical picture, was the so-called "tilt test", little-known to general medical practice, as well as the laboriousness of making a final diagnosis of the long *QT* Syndrome type 2, which required a molecular genetic study — whole-exome sequencing. Patient S. had vasovagal syncope that not associated with long *QT* syndrome, but she has a risk of sudden cardiac death, and the article identifies therapeutic and other measures to reduce this risk.

Keywords: long *QT*, syncope, tilt test, whole-exome sequencing

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To date, the genetic nature of the hereditary long *QT* interval (LQT) syndrome has been proven, with clear diagnostic criteria [1]. The characteristic signs on electrocardiogram (ECG) include *QT* interval elongation and ventricular tachycardia paroxysms [2]. The clinical manifestations of LQT syndrome are typical and are characterized by repeated episodes of loss of consciousness due to polymorphic ventricular tachycardia, mainly of the "torsades de pointes" type.

The high incidence of sudden cardiac death in affected families made LQT syndrome one of the most significant among pathological conditions, and it is identified as the optimal model for investigating sudden cardiac death [3]. The development of typical clinical manifestations of the hereditary LQT syndrome is associated with various genes, of which at least 12 have now been identified [4, 5]. A mutation was found in one of the genes, and their protein products are transmembrane ion-selective channels and membrane components. The changes are accompanied by a loss of potassium channel functions with a delayed repolarization (LQT1, LQT2, LQT5, LQT6, and LQT7) or an increase in the functions of sodium (LQT3) or calcium (LQT8) channels, leading to a delay in repolarization currents.

The urgency of the problem of LQT syndrome is related to the lack of awareness of pediatricians, therapists, neuropathologists, and even cardiologists about this syndrome, which can often result in medical errors. The similarity of the clinical manifestations of LQT syndrome with classical epileptic seizures often contributes to the overdiagnosis of epilepsy [3], which can often lead to sudden cardiac death in patients with LQT syndrome, whose condition is interpreted incorrectly, despite regular visits to specialists.

ECG can reveal congenital or acquired LQT, which it causes ventricular tachycardia (manifested by fainting, in some cases progressing into ventricular fibrillation and patient's death). Moreover, a patient with LQT may have fainting that is not associated with an electrical pathology of the heart

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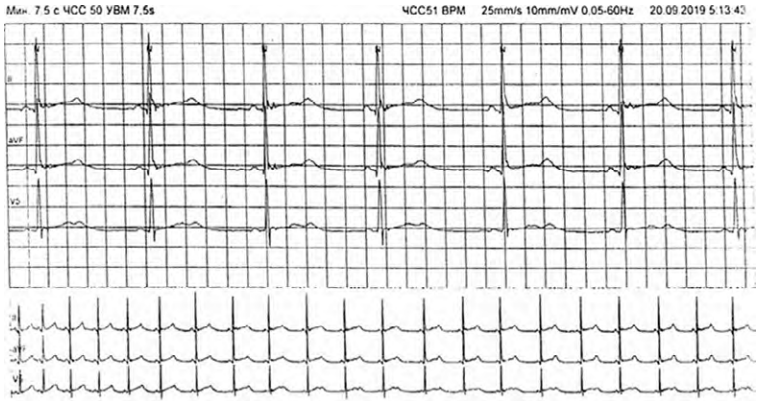

Fig. 1. Holter monitoring of the electrocardiogram of Patient S. T wave alternation.

but caused by various, primarily neurological pathologies.

This report presents the case history of a 33-year-old female patient (Patient S), who had syncope since age 15 years, and congenital LQT. It could be established only with a long-term clinical and instrumental study.

From age 14 years, the patient consulted with a cardiologist because of LQT on the ECG. At the first episode, she lost consciousness at age 15 years after prolonged exposure to the sun. The next episode of syncope occurred at age 32 years (in 2018) in a stuffy bus. At the third episode, she lost consciousness at age 33 years (in 2019) when changing her body position, experiencing darkened vision, ear buzzing, and severe headache. According to her husband, her face darkened, and her arms were bent at the elbows. She was unconscious for 1.5–2.0 min. When she regained consciousness, she felt well and had no memory lapse. During all three syncope episodes, she had involuntary urination.

Epilepsy was ruled out after 2-h sleep electroencephalography (EEG). After the EEG, when standing up, she experienced signs of presyncope (i.e., ear buzzing, darkened vision, and headache). She lost consciousness for the fourth time.

At discharge, her diagnoses were autonomic dysfunction syndrome, asthenoneurotic syndrome with repeated syncope, long QT syndrome, and syncope of unspecified genesis.

For the fifth time, syncope occurred on December 02, 2019, when assuming an upright position, and she experienced ear buzzing, tinnitus, and severe dizziness. She was unconscious for 1 min; at 10 min after it, she could not understand what had happened to her.

Family history and heredity. The patient's mother died at age 48 in her sleep (presumably from sudden cardiac death). Her mother had arterial hypertension and episodes of loss of consciousness, arising in the supine position; at rest, lasting 5 min, she recovered independently, and relatives gave her artificial respiration. Her ECG was not available. The older sister (36 years old) and her children had no pathologic ECG findings.

Physical examination. The general condition was satisfactory. She was normostenic. Her height, body weight, and body mass index were 163 cm, 55 kg, and 20.7 kg/m^2, respectively. The skin was pink. The heart had clear tones. The pulse rate was 85 beats per minute, regular, with satisfactory quality. The blood pressure was 108/90 mm Hg.

Biochemical blood test from December 14, 2019: potassium, 4.34 mmol/L; sodium, 134.6 mmol/L; chlorides, 104.0 mmol/L; magnesium, 0.85 mmol/L; ionized calcium, 1.25 mmol/L. Levels of thyrotropic hormone, triiodothyronine, and thyroxine were normal.

Data regarding the *QT* interval over time: The corrected *QT* interval (*QTc*) values were 517 ms (12/2/2019), 520 ms (12/3/2019), and 496 ms (12/5/2019). With Holter ECG monitoring, the *QTc* was 583 ms. The *QTc* during administration of beta-adrenergic blocking agent (BAB) (metoprolol succinate 25 mg) was 483 ms. As Patient S. had an arterial pressure of 90/60 mm Hg, the BAB dose was increased gradually.

The Holter ECG monitoring from September 19, 2019, duration of 22 h 29 min, showed sinus rhythm, maximum heart rate of 166 beats per minute; *QT*, 289 ms; minimum heart rate, 50 beats per minute; *PQ*, 131 ms; *QT*, 558 ms. Ectopic activity has not been recorded. Throughout the study, an alternation of the *T* wave was recorded. The pattern of early repolarization of the ventricles was noted. Heart rate variability indicators were normal (Fig. 1).

During the study, no epileptiform activity, epileptic seizures, and EEG patterns were recorded on video EEG monitoring on September 15, 2019,

for 2 h in a state of active and passive wakefulness, sleep and with functional tests. On the electroencephalogram from September 20, 2019, focal and paroxysmal changes were not recorded. X-ray computed tomography and magnetic resonance imaging of the brain on September 18, 2019, did not show pathology. Visualization of the extracranial part of the brachiocephalic arteries of the brain on September 18, 2019, did not show pathology.

The tilt test on December 19, 2019, with passive orthostasis did not induce syncope. On December 24, 2019, a repeated tilt test with passive orthostasis was performed according to the Italian protocol at minute 2 after inhalation of nitrospray (0.4 mg). Subsequently, a mixed vasovagal presyncope developed, which manifested as dizziness, darkened vision, a decrease in heart rate from 135 to 41 beats per minute, and a decrease in systolic blood pressure to 85 mm Hg and diastolic up to 0.3 mm Hg.

Thus, Patient S had a combined pathology of LQT syndrome but without cardiac arrhythmias and vasovagal syndrome manifested by fainting (syncope).

The most important stage in the examination of Patient S was a genetic study. Genes potentially related to the patient's disease were analyzed for their influence on the structure and function of the protein in accordance with the recommendations of the American College of Medical Genetics and Genomics [6]. According to the results of full-exome sequencing, a unique duplication in a heterozygous state in the *KCNH2* gene ENST0W00262186.5:c.2676_2680dup was revealed, leading to a shift in the reading frame and the formation of a premature stop codon NSP00000262186.5:p.Arg894ProfsTer82. Mutations leading to the haploinsufficiency of the HERG protein as a result of premature stop codons in kcnh2 mRNA represent a typical and well-known mechanism for the development of type 2 LQT syndrome.

The following recommendations were offered to Patient S.

1. Limitation of physical and emotional stress.

2. Drugs that prolong the *QT* interval are not indicated throughout life.

3. Monitoring of potassium levels (once every 6 months or immediately when palpitations or fainting appear). It is recommended to consider prescribing KCl *per os* or spironolactone in addition to constant therapy with BAB.

4. Consultation with a cardiac surgeon-arrhythmologist to determine the possibility and time of implantation of a cardioverter-defibrillator.

5. Cascade family screening of relatives of the first and second kinship.

During repeated examinations, Patient S reported satisfactory outcomes. Fainting did not occur anymore. She controls the process of getting up; at first, she necessarily sat down and then got up. She takes BAB (metoprolol succinate), starting with a dose of 12.5 mg, increasing every week by 12.5 mg. She is currently taking 162.5 mg per day and is suggested to increase the dose to 200 mg per day. She associates sleep disturbance with the intake of BAB, namely, difficulty of falling asleep and waking up in the middle of the night. Blood pressure against the intake of BAB was 90/60 mm Hg, and pulse rate was approximately 70 beats per minute. While taking BAB, the duration of prolonged *QTc* did not decrease and remained at approximately 544 ms (after effective treatment with BAB, the *QTc* remains elongated, but the *QTc* dispersion decreases in "responders").

Thus, the examination of patients with LQT and syncope should be comprehensive. Its algorithm should include research methods that enable recognition of the nature of syncope not associated with LQT. A genetic study, that is, complete genomic sequencing to determine the type of LQT, is required. This helps in providing recommendations for lifestyle changes and drug therapy. The implantation of a cardioverter-defibrillator will prevent sudden cardiac death in a patient.

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