CASE REPORT

The importance of the epinephrine provocation test for the hidden type-1 congenital long QT syndrome

Gizli tip 1 konjenital uzun QT sendromunda epinefrin provokasyon testinin önemi

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Summary– Congenital long QT syndrome (LQTS) is a genetic channelopathy associated with a high incidence of sudden cardiac death in children and young adults. QT interval prolongation is typically the primary finding on the electrocardiography (ECG) recordings, but a normal QT interval may be seen in as many as 40% of patients with LQTS due to incomplete penetrance. A normal QT interval on ECG in patients with LQTS is known as hidden LQTS. An epinephrine provocation test can help in the diagnosis of hidden LQTS. This case report describes the use of an epinephrine provocation test to diagnose hidden LQTS in 3 patients who had normal QT interval and corrected QT interval on ECG and a family history of sudden cardiac death.

Özet– Konjenital uzun QT sendromu (UQTS) çocuklarda ve genç erişkinlerde ani kardiyak ölüm insidansı ile ilişkili genetik bir kanalopatidir. QT aralığı uzaması elektrokardiyografide (EKG) ana bulgudur, ancak eksik penetrasyon nedeniyle UQTS hastaların yaklaşık %40'ında normal QT aralığı görülür. UQTS'li hastalarda EKG'de normal QT aralığı gizli UQTS olarak bilinmektedir. Epinefrin provokasyon testi gizli UQTS tanısında yardımcı olabilir. Bu olgu serisinde EKG'de normal QT ve düzeltilmiş QT aralıkları olan ve ailesinde ani kalp ölümü öyküsü olan üç bireyde gizli UQTS tanısı için epinefrin provokasyon testi kullanıldı.

Long QT syndrome (LQTS) type 1 is a congenital cardiac disorder in which abnormalities in the KCNQ1 gene, a voltage-gated potassium channel, cause life-threatening cardiac arrhythmias.[1] Congenital LQTS is characterized by a prolonged QT interval on an electrocardiogram (ECG), which may lead to sudden cardiac death secondary to cardiac arrhythmias.[2] In symptomatic patients, the 1-year mortality rate after t he first syncope attack has been reported to be 21%.[3] LQTS demonstrates phenotypic and genetic heterogeneity.[4] However, in some LQTS cases, a prolonged QT interval may not be detected.[5] Incomplete penetrance of the gene can lead to the corrected QT (QTc) interval appearing normal on an ECG.[6] Provocation tests, particularly an epinephrine provocation test (EPT), can be helpful in a diagnosis of hidden LQT1.[7] In this case series, an EPT was performed on 3 siblings who had normal QT and QTc intervals on an ECG. The aim of this study was to show that an EPT can play an essential role in the diagnosis of hidden LQT1.

Abbreviations:

ECG	*Electrocardiogram*
EPT	*Epinephrine provocation test*
IKr	*Rapidly activating delayed rectifier potassium channel*
IKs	*Slowly activating delayed rectifier potassium channel*
LQTS	*Long QT syndrome*
PCR	*Polymerase chain reaction*
QTc	*Corrected QT interval*

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The parents had a consanguineous marriage. They had 8 children, 3 of whom had died at 15, 18, and 19 years

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of age (Fig. 1). The parents brought 3 of their children to the outpatient clinic for a detailed cardiac examination. There was no history of syncope or palpitations reported among the patients' family members (including the deceased siblings). The patients had normal clinical examination results, their biochemical parameters were within normal limits, and there was no structural heart disease observed on echocardiography or magnetic resonance imaging. Exercise ECGs and 72-hour rhythm Holter analysis also showed normal results. An ajmaline test to rule out Brugada Syndrome was also performed with a "negative" result. Blood samples were sent to the genetics laboratory for LQTS diagnosis. An epinephrine QT provocation test was performed based on the Mayo Clinic protocol.[8] After a 10-minute rest, vital signs and ECG parameters (QT and RR intervals) were recorded. In each stage, the QT and QTc intervals were measured at least 3 times in the V5 derivation, then averaged and recorded. The QT intervals were measured using a digital caliper (Fig. 2), and the QTc was obtained using the Bazett formula. An epinephrine infusion was started with an initial dose of 0.025 μg/kg/minute for the first 10 minutes. No dynamic changes were noted on the ECG after 10 minutes. The epinephrine infusion dosage was then increased to 0.05 μg/kg/minute, 0.1 μg/kg/minute, and 0.2 μg/kg/minute at 5-minute intervals. The dosage did not exceed 0.3 μg/kg/minute, due to possible side effects. The epinephrine infusion lasted for a total of 25 minutes. An increase of more than 30 milliseconds in QTc intervals during the EPT was considered abnormal. A QTc prolongation was reported in 2 patients during the EPT. Figures 3 and 4 show the patients' ECG changes. Table 1 summarizes the 3 patients' demographic, genetic, and EPT data. After diagnosis, beta-blocker (metoprolol succinate) treatment was initiated. The patients were advised to avoid the use of drugs that prolong QTc interval, as well as swimming, diving, and similar sports, and they were discharged without any complications.

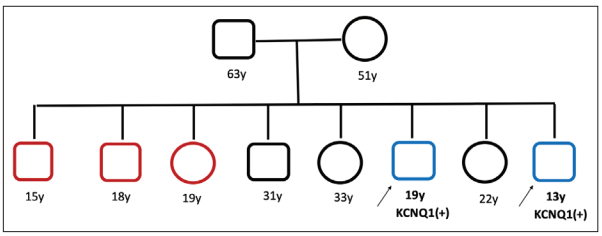

Figure 1. A family pedigree of 2 brothers with hidden long QT syndrome. The patients are indicated by the blue squares and arrows. Red symbols represent the siblings who suffered sudden cardiac death.

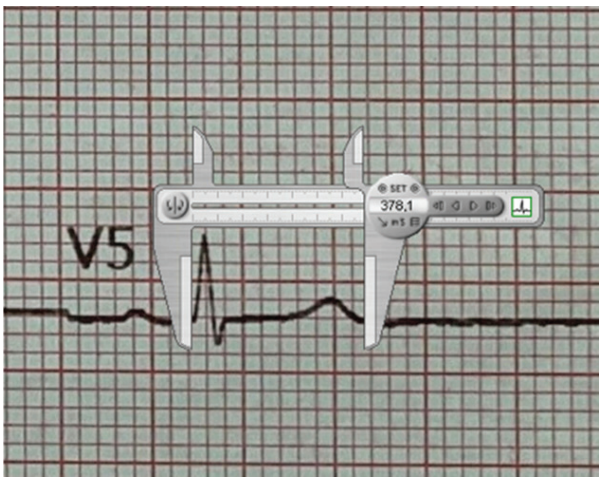

Figure 2. QT intervals were measured using a digital caliper.

DNA isolation and genetic analysis

The DNA isolation was performed using blood samples and a QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). The DNA isolation samples were stored at -20°C until polymerase chain reaction (PCR) analysis could be performed. The primary target was

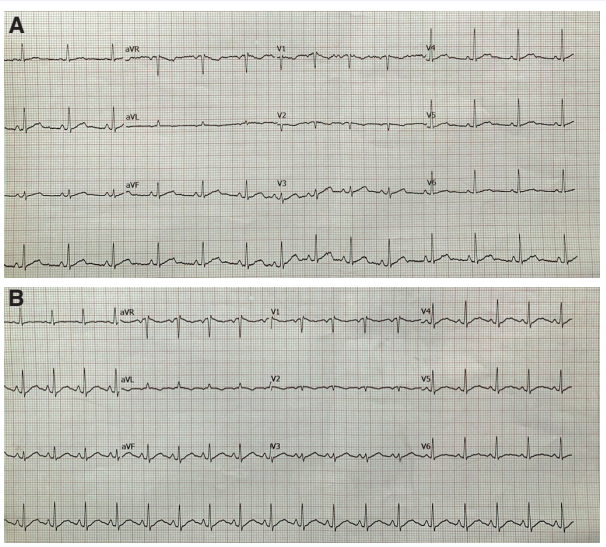

Figure 3. Electrocardiogram results of patient with KCNQ gene mutation, **(A)** Basal electrocardiography obtained before the epinephrine provocation test (QTc 404 milliseconds, Bazett formula); **(B)** Electrocardiography obtained at the 22nd minute of the epinephrine provocation test (QTc 556 milliseconds, Bazett formula).

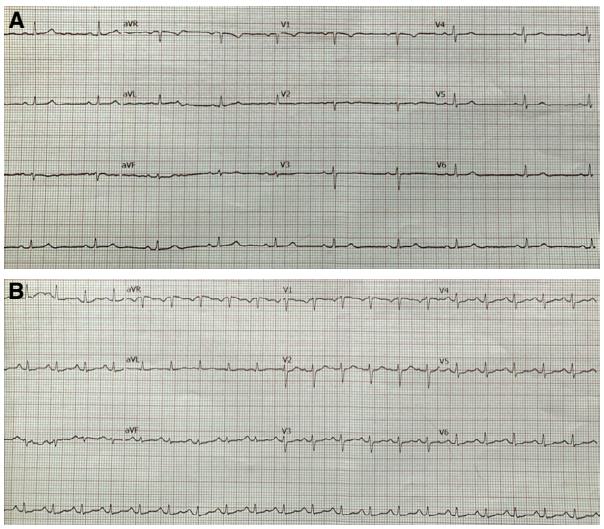

Figure 4. Electrocardiogram results of a patient with KCNQ gene mutation. **(A)** Basal electrocardiography obtained before the epinephrine provocation test (QTc 397 milliseconds, Bazett formula); **(B)** Electrocardiography obtained at the 16th minute of the epinephrine provocation test (QTc 575 milliseconds, Bazett formula).

18 gene-encoding regions, and exon-intron boundaries were amplified by PCR. The 18 gene regions were ANK2, AKAP9, CAV3, CACNA1C, CACNB2, GPD1L, HCN4, KCNJ2, KCNQ1, KCNE1, KCNE2, KCNE3, KCNH2, SCN1B, SCN5A, SCN4B, SNTA1, and SCN3B. Amplification of the analyzed gene regions was obtained from DNA extraction. No KCNQ1 gene mutation was noted in patient 3, and a heterozygote mutation in the KCNQ1 gene was detected in patients 1 and 2. The KCNQ1 gene encodes the alpha subunit of the voltage-gated potassium channel, which moves potassium ions out of the cell during the third phase of action potential.

DISCUSSION

Congenital LQTS can cause lethal arrhythmias, such as torsades de pointes, ventricular fibrillation, syncope, and sudden cardiac death.[1] Genetic screening can detect disease-causing mutations in 75% of LQTS patients. Three genes have been demonstrated in 90% of these mutations: LQT1-KCNQ1, LQT2-KCNH2, and LQT3-SCN5A.[9] LQT1 patients are sensitive to sympathetic stimulation, which is the main trigger, while LQT2 and LQT3 patients are more sensitive to bradycardia conditions. While sports activities requiring strenuous effort, such as swimming, can trigger arrhythmia in LQT1 patients, high noise ex-

Table 1. The demographic, genetic, and clinical data of the patients

Cases	Case-1	Case-2	Case-3
Genetic mutation	KCNQ1	KCNQ1	Negative
Age (years)	13	19	22
Gender	Male	Male	Female
Weight (kg)	35	75	60
Heart rate (bpm)	78	64	70
Systolic blood pressure (mm Hg)	110	120	100
Diastolic blood pressure (mm Hg)	70	70	70
Echocardiography	Normal	Normal	Normal
Magnetic resonance imaging	Normal	Normal	Normal
Exercise stress test	Normal	Normal	Normal
Rhythm Holter (72 hours)	Normal	Normal	Normal
Ajmaline test	Negative	Negative	Negative
EPT duration (minutes)	22	16	25
MEID (ug/kg/minutes)	0.2	0.1	0.2
Basal QTc (msn)	404	397	389
Second QTc (msn)	550	575	381
Medication	Metoprolol succinate	Metoprolol succinate	(–)

EPT: Epinephrine provocation test; MEID: Maximum epinephrine infusion dose.

posure may cause arrhythmia in LQT2 patients, and arrhythmia usually occurs during sleep in LQT3 patients.[10] The genetic mutation may affect the sodium and potassium channels; thus, sodium input into the cell increases and potassium output from the cell decreases. Due to the electrolyte imbalance inside the cell, QT prolongation may be seen during an ECG as a sign of repolarization and depolarization extension abnormality. However, in hidden LQTS patients, QT prolongation may not be observable on the ECG. Due to the high incidence of hidden LQTS, sensitive and specific diagnostic provocation tests are needed. Genetic tests to diagnose LQTS have been identified.[11] However, a gene mutation is not always associated with LQTS; hence, an EPT can play an essential role in the diagnosis. The results of the EPT in hidden LQTS patients were similar in LQTS patients who had a QT prolongation during a resting ECG.[12] The EPT test has a 91% sensitivity, 83% specificity, 72% positive predictive value, and 95% negative predictive value for LQTS diagnosis. Thus, this report used an EPT to diagnose hidden LQTS in our patients.

Epinephrine increases inotropy and chronotropy in the normal heart. The slowly activating delayed rectifier potassium (IKs) channels control the repolarization of the heart muscle. During the third phase of action potential, the IKs channel moves the potassium ions out of the cell. As the activity of the IKs increases, the QT interval shortens, with a decreasing action potential time.[13] This physiological effect explains the shortened QT interval during epinephrine infusion. Sympathetic stimulation does not activate the IKs in patients with a KCNQ1 mutation (LQT1). These patients have prolonged repolarization of the action potential because of the KCNQ1 mutation and as a result, a prolonged QT interval is seen in the EPT. Therefore, a positive EPT may indicate LQT1. Patients with a KCNH2 mutation (LQTS2) have rapidly activating delayed rectifier potassium (IKr) channels. IKr channels represent a small portion of the potassium channels which are responsible for phase 3 repolarization and are not as sensitive as sympathetic IKs channels. Thus, during an EPT in LQT2 patients, transient action potential prolongation may occur. After this prolongation, the action potential duration normalizes, and absolute QT intervals shorten due to normal-functioning IKs. This transient prolongation and subsequent QT interval shortening is a characteristic feature of the LQT2 phenotype.[14] Furthermore, LQT3 phenotypes are characterized by a constant reduction of the action potential duration with an EPT caused by IKs channel stimulation and increased sodium inflow into cells.[15] Therefore, a positive EPT can hypothetically diagnose LQT1 syndrome (paradoxical 30-millisecond QT response during low-dose epinephrine infusion). An EPT also provides additional information to determine the LQTS type and treatment options in patients with a normal QT interval.

Beta-blocker therapy is the first-line treatment for LQTS.[16] Although no randomized clinical trials have determined which beta-blocker agent yields the best outcome in LQTS patients, currently, nadolol is the first treatment option for LQTS.[17] Moss et al.[18] evaluated 1530 LQTS patients in the International Registry of LQTS. In this study, when the LQTS genotypes were grouped together, atenolol, metoprolol, propranolol, and nadolol all appeared to be equally effective. A preference for nadolol as a first choice agent has been established among experts; however, no conclusive recommendation is available to identify the next best option.[17] Our patients were treated with metoprolol succinate because nadolol was unavailable in our country.

In conclusion, following a detailed physical examination and an ECG in patients with a family history of sudden cardiac death at a young age, the EPT can safely add to the diagnosis of hidden LQTS. An EPT is an inexpensive and easily accessible method, and therefore, it can be considered as technique to arrive at an LQTS diagnosis in cardiology centers until genetic examination results are obtained.

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Keywords: Hidden long QT syndrome; epinephrine provocation test; sudden death

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