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Case Report

Concealed Long-QT Syndrome with Rare KCNQ1 Gene Mutation in an Elderly Female: A Case Report

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Abstract

Long QT syndrome (LQTS) is a hereditary disorder that can lead to recurrent syncope, convulsive episodes, and sudden death due to ventricular arrhythmia. In most instances, LQTS remains concealed and primarily presents as unexplained syncope despite have a normal electrocardiogram (ECG) during periods of rest. This characteristic can be highly deceptive and may result in severe and potentially fatal consequences if treated incorrectly. In this report, we present a case of concealed LQTS in an elderly female patient who experienced an initial episode of syncope at the age of 76. Upon admission, the surface ECG showed no abnormalities. However, during the bedside ECG examination, typical manifestations of LQTS were detected, indicating an early stage of the ictal process. Subsequent treatment with β-blockers provided symptomatic relief. Genetic testing identified a rare mutation, p. Arg366Trp (with a c.1096C>T variant), in the *KCNQ1* gene, confirming the diagnosis of LQTS. Although congenital LQTS cases are more commonly found in young females, the potential for LQTS should not be overlooked in elderly patients who complain of unexplained syncope, even if their ECG normal. The use of an artificial intelligence (AI)-based diagnostic tool has the potential to offer a more precise means of identifying concealed LQTS in the future, but, until now, thorough examination and close observation during admission is necessary to avoid missed diagnoses of the concealed LQTS-syndrome.

Keywords

long QT syndrome; KCNQ1; electrocardiogram

Introduction

Long QT syndrome (LQTS) is an arrhythmogenic disease with a genetic predisposition clinically characterized by prolonged QT interval and an abnormal T wave on the surface electrocardiogram (ECG), recurrent syncope, and sudden cardiac death. Since the first cases of Long QT syndrome were reported in 1957, advances in genetic cardiology and cardiac electrophysiology, coupled with the widespread adoption of gene detection, have greatly enhanced the understanding of this inherited cardiac condition. Congenital LQTS is closely associated with the pathogenetic mutation in the gene encoding the cardiac ion channel, which leads to the disturbance of myocardial ionic equilibrium and subsequent pathological myocardial electrical activity [1]. Genome-wide association studies have shown that the great majority of congenital LQTS can be divided into three subtypes: LQT1, LQT2, and LQT3, corresponding to the mutations in *KCNQ1*, *KCNH2*, and *SCN5A* respectively [2].

Due to the predominantly young age of individuals affected by this genetic cardiac condition, previous studies have primarily focused on the incidence of LQTS in the younger patients [3]. Nonetheless, congenital LQTS can occur at any age during a person's lifetime [4]. Aged patients with LQTS are more prone to misdiagnosis due to an increased risk of other cardiovascular diseases. This is because the clinical symptoms of LQTS can be masked by cerebral ischemic events caused by organic lesions. In this report, we present the case of an elderly patient who experienced concealed LQTS with a rare mutation in the *KCNQ1* gene. The patient initially suffered from syncope at the age of seventy-six, following persistent headache and dizziness. Unfortunately, the normal appearance of the ECG upon admission, as well as a history of stroke and hypertension, concealed the true cause of syncope in this patient. After ruling out cerebral occupying lesions and new ischemic injury through magnetic resonance imaging (MRI), the diagnosis of LQTS was ultimately confirmed using a surface ECG during an episode of palpitations.

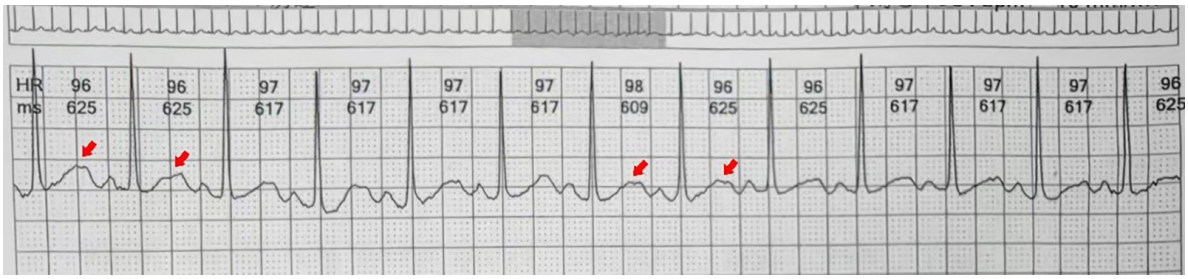

Fig. 1. The sporadic QT interval prolongation found on 24 h dynamic ECG (25 mm/s, 10 mm/mV). Average heart rate 97 bpm, QTc interval of 559 ms. Red arrow indicated the typical T wave notching. ECG, electroencephalogram; QTc, QT interval; HR, heart rate.

Case Presentation

A 76-year-old female was admitted to our emergency department with a persistent headache and dizziness associated with nausea and vomiting, and a sudden syncopal episode which resolved on its own after a few minutes.

The patient was conscious on admission with only recurrent episodes of headache and dizziness. She had a complex medical history for uncontrolled hypertension, stroke and unproven coronary artery disease (self-reported), indicating a high risk of cardiovascular events. She had no history of seizures or other neurological conditions and was not taking medications that could cause cardiac arrhythmias. Remarkably, all three of her sons experienced similar unexplained fainting spells during their childhood (two of them are still alive). On examination, the patient's pupillary reflex to light and other neurological physical examinations were unremarkable. There was no fever or neck stiffness. There was no limb numbness or incontinence. On admission, her blood pressure was 179/74 mmHg. An emergency computed tomography (CT) scan of the brain suggested old cerebral infarction and cerebral atrophy. The electrocardiogram on admission showed no abnormal changes.

The admission diagnosis included unexplained headache and syncope, hypertension (very high risk), and coronary artery disease (not yet confirmed). At this stage, epilepsy, brain-occupying lesions, cerebrovascular disease, intracranial infections and hypertensive encephalopathy were considered as possible triggers of headache and syncope. Subsequently, she was referred to the Department of Neurology for further examination and treatment.

Brain disease in this patient was ruled out due to a negative EEG, laboratory tests and MRI. A 24-hour ambulatory electrocardiogram (Fig. 1) showed a prolonged sporadic QT interval with a heart rate-corrected QT interval (QTc) of 559 ms (normal range 320–450). The results of the electrolyte analysis showed a potassium of 3.78 mmol/L, a calcium of 2.13 mmol/L, a sodium of 143.8 mmol/L, and a chloride of 104 mmol/L. CT angiography also confirmed the diagnosis of coronary artery disease. This new evidence led us to consider the possibility of cardiogenic syncope.

Additional evidence pointing to LQTS appeared on the morning of the third hospital day. The patient developed palpitations, dyspnea and tremor of the extremities, while the surface ECG showed sinus rhythm, a prolonged QT interval (QTc of 720 ms), typical T-wave tangents and inversions, but no ST-T changes (Fig. 2). She was immediately treated with a combination of potassium, magnesium, and beta-blockers, and her symptoms resolved.

Subsequently, genetic testing was performed on the patient and her second son, which showed the rare mutation p. Arg366Trp (c.1096C>T variant) in the *KCNQ1* gene (NM_000218) associated with LQTS type 1 (LQT1). The diagnosis of LQT1 was reconfirmed (Fig. 3) [5].

Due to financial constraints, the patient refused to have an implantable cardioverter defibrillator (ICD) implanted, which would have prevented further episodes. After one week of observation, the patient was discharged from the hospital with follow up, including regular monitoring of blood pressure and lipid levels, as well as treatment with oral β-blockers and statins. The patient was also advised to avoid medications that prolong the QT interval.

Discussion

LQTS is a heritable cardiac electrophysiologic disorder clinically manifesting with syncope, vulnerable to malignant arrhythmia, sudden death, and a variety of ECG features, including QT interval prolongation and T-wave abnormalities [6]. The primary diagnosis of LQTS is determined by Schwartz's score, which includes the patients' electrocardiographic findings, clinical history, and family history [7]. A score higher than 3.5 points is a positive score suggesting a high suspicion for LQTS. However, although medications that prolonging the QT interval may induce LQTS, the hereditary ion channel disturbance is still regarded as the leading cause of LQTS [8]. Nearly 75% of the clinically LQTS were associated with three common gene variants, with a rate of 30%–35% for *KCNQ1* (LQT1), 25%–40% for *KCNH2* (LQT2), and 5%–10% for *SCN5A* (LQT3) [9]. Therefore, a genetic test can confirm the definite diagnosis and disease classification.

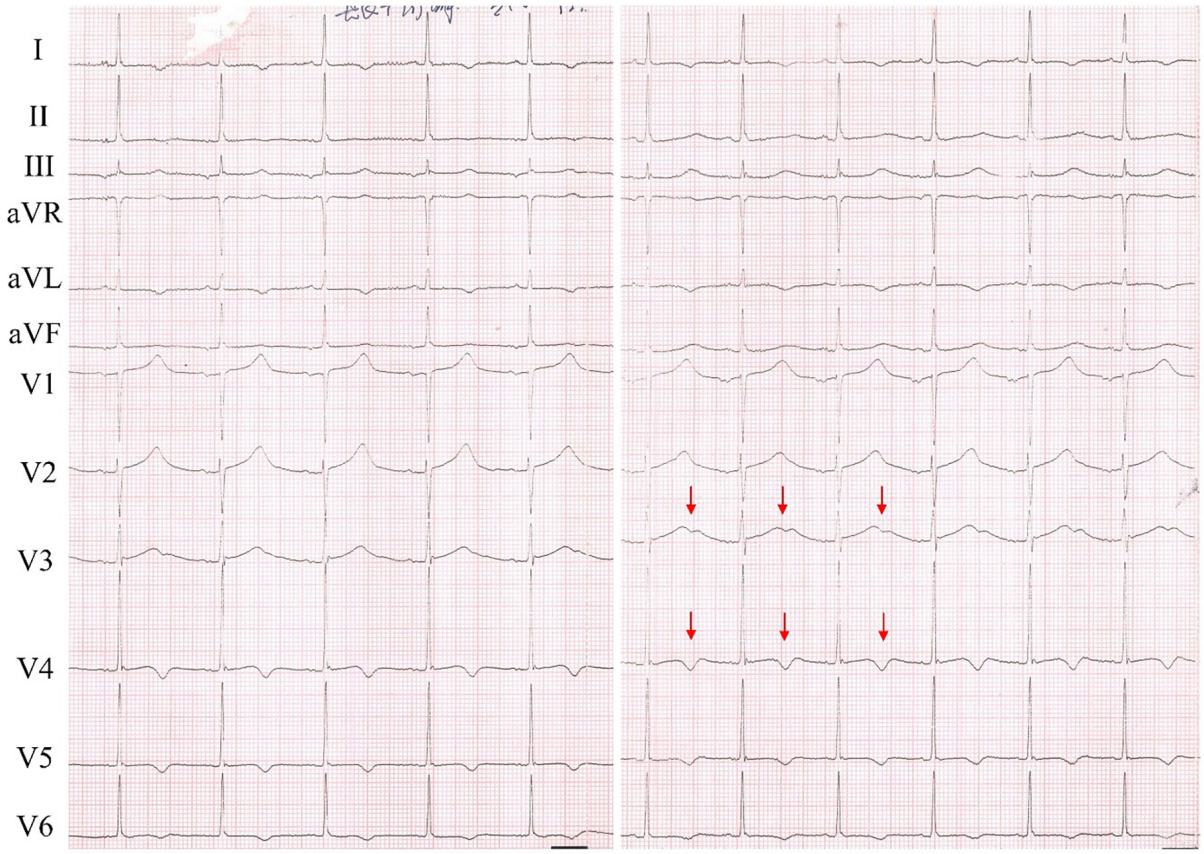

Fig. 2. The bedside ECG during an attack on the morning of third hospital day. Average heart rate 68 bpm, QTc interval of 720 ms. Red arrow indicated the typical T wave notching and inversion.

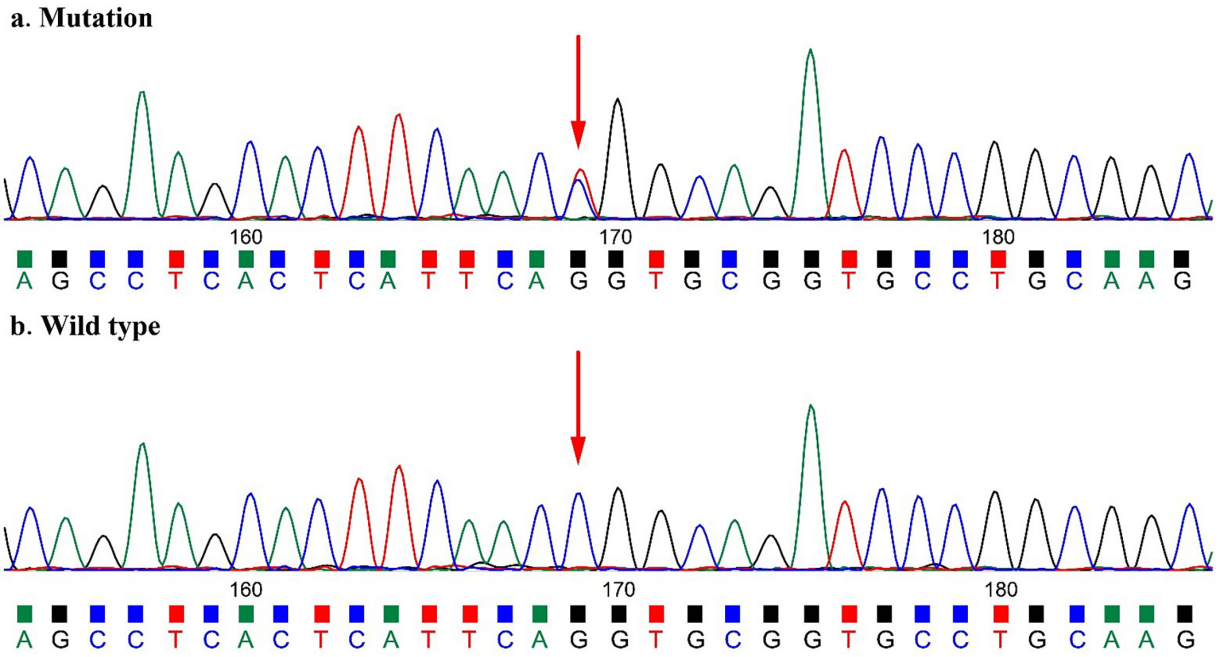

Fig. 3. High throughput sequencing of patient and her family members. The DNA sequence of *KCNQ1* showed a c.1096C>T heterozygous variant, resulting in a p. Arg366Trp substitution and vulnerability of LQTS, which happened to in the patient and her second son (a) but not in other family members (eldest son and grandchildren) (b). DNA, Deoxyribonucleic acid; LQTS, Long QT syndrome.

It has also been reported that LQTS patients with the causative mutation may be asymptomatic [10]. Patients with concealed LQTS may show a normal ECG at rest. However, a favorable genotype is associated with an increased risk of arrhythmia and sudden cardiac death. This condition is also known as normal QT interval LQTS or genotype-positive/phenotype-negative LQTS [11]. Although clinical tests such as adrenaline challenges and explosive cycling have been proposed to help diagnose occult LQTS, early recognition and diagnosis by clinicians, remain challenging when these patients present with unexplained syncope, and a normal ECG [12,13]. Recently, the use of artificial intelligence (AI) for ECG analysis has been proposed to diagnose acquired and congenital LQTS [14,15]. The convolutional neural network (CNN) model, which refers to a primary branch of AI algorithm and mainly applies to visual image recognition, shows higher sensitivity and accuracy for an ECG-based LQTS diagnosis compared to measuring corrected QT intervals (QTc). Notably, AI-enhanced ECGs have also shown potential for significant improvements in the diagnosis of acquired and congenital LQTS. Bos *et al*. [16] reported that a CNN model predicted LQTS with an accuracy of nearly 80% when applied to the ECG. In addition, a retrospective study shows that a new AI architecture called the Xception Time model outperforms previous full convolutional network models in identifying cryptic LQTS (91.8% and 83.6% equilibrium accuracy, respectively) [17]. These models demonstrated strong performance in the ECG diagnosis of occult LQTS, and it is particularly noteworthy that the two studies were conducted only a year and a half apart. With the rapid development of artificial intelligence and deep learning in the field of medical image recognition, patients with occult LQTS can benefit greatly from early diagnosis and preventive treatment.

In this case, the patient was admitted to the hospital with syncope after headache and dizziness, which suggested a cerebrovascular etiology or a brain-occupying lesion, especially for a 76-year-old female with no history of seizures. The misleading symptoms led to a delay in diagnosis putting the patients at risk for malignant arrhythmia for a few days after admission. Fortunately, we detected the prolonged ST interval and made the correct diagnosis prior to any adverse events. As mentioned above, the AI-enhanced ECG seems to be a promising solution for the concise and expeditious diagnosis of concealed LQTS. However, current AI models were trained by the ECG images with normal backgrounds, and there is no evidence to support the diagnostic accuracy and sensitivity of these models in an ECG image with persistent abnormal changes, such as persistent atrial fibrillation and an old myocardial infarction. Further research is needed to determine the diagnostic value of AI models in concealed LQTS patients with complicated ECGs. Since it was difficult for this patient to adhere to drug therapy, we proposed the implantation of an ICD. However, it is still controversial for the application of ICD in LQT1 patients with an extremely long QTc (>500 ms). For most adult patients with LQT1, β-blocker therapy is sufficient, and ICD implantation is not recommended [18]. However, a recent comparative study verified that ICD therapy may decrease the risk of all-cause mortality for patients with syncope and QTc $\geq$500 ms [19].

Conclusions

We report an elderly female patient with concealed LQT1 carrying a single *KCNQ1*-Arg366Trp mutation. Clinicians should be aware of the potential for LQTS in elderly patients presenting with syncope of unknown etiology. In the future, AI may offer the ability to diagnose concealed LQTS more rapidly and avoid unnecessary adverse outcomes in these patients. The CARE checklist was used when writing this case report (**Supplementary Table 1**).

Availability of Data and Materials

The original contributions presented in the study are included in the article/supplementary material, and further inquiries can be directed to the corresponding author.

Author Contributions

JZ and CZ are co-first authors; CZ and JZ performed the literature search and screening; PZ and YH analyzed and interpreted the data; JZ and JY were involved in the conceptualization and design of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.59958/hsf.6803.

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