Computerized Misinterpretation of QT Interval in 12-Lead Electrocardiogram and Its Clinical Consequences: A Case of Recurrent Syncope

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1. Abstract
The diagnosis of long QT syndrome may be delayed due to absence of electrocardiogram (ECG) examination and/or QT interval misdiagnosis. We present the case of a patient who took 8 years before being diagnosed with long QT syndrome. Despite the presence of marked QT prolongation and bimodal T waves, automated ECG recording misdiagnosed the patient to be normal. The patient had recurrent syncope; however, repeat ECG examination was not performed because her initial ECG was considered normal. It is crucial in cases of syncope that multiple ECG examinations and physician assessment of findings are performed, without relying exclusively on an automated ECG diagnosis.

2. Abbreviations: ECG: Electrocardiogram; QTc: Corrected QT Interval; Tdp: Torsades De Pointes

3. Introduction
Patients with cardiac syncope have increased risk of death [1], and the occurrence of “syncope” is an important indicator of arrhythmic risk [1-3]. Patients with unexplained syncope may have hidden long QT syndrome (LQTS) [2]. Although electrocardiogram (ECG) is important for the diagnosis of LQTS, the diagnosis may be delayed due to absence of ECG examination and/or difficulties of QT interval evaluation [2]. Automated ECG diagnosis has the benefit to reduce the effort of physician for ECG evaluation [4]. However, the automated ECG diagnosis are not always correct, in particular, QT interval [5]. We present the case of a patient...
for whom LQTS diagnosis took 8 years. Despite the presence of marked QT prolongation and bimodal T waves, automated ECG diagnosis misdiagnosed the patient to be normal at the first syncope. The patient had recurrent syncope; however, repeat ECG examination was not performed.

4. Case Report

A 27-year-old female visited our emergency room in the middle of the night because she experienced syncope several times throughout the preceding 2 days upon waking up and when attempting walking at night. At the time of the visit, her consciousness level was clear and plasma potassium concentration was 4.0 mEq/L (normal range: 3.6–4.8 mEq/L). Her 12-lead electrocardiogram (ECG) revealed sinus rhythm (65 beats/min) and QT prolongation with low amplitude T waves (QT/QTc [intervals], 600/640 ms) (Figure 1A). Echocardiography, chest X-ray, and brain magnetic resonance imaging (MRI) findings were normal. She was admitted for follow-up due to the presence of marked QT prolongation on 12-lead ECG. Five hours after the admission, torsades de pointes (TdP) spontaneously occurred with typical initiating “short-long-short” sequences (Figure 1B) when she felt faintness. Therefore, the patient was clinically diagnosed with long QT syndrome. She had no abnormal ECG findings in past school physical examination. She had no family history of syncope, sudden death, or long QT syndrome (Figure 2A). ECGs of her mother and son showed no QT prolongation (Figure 2A). At the age of 19, the patient expe-
rienced nightmares during sleep, which were followed by convulsions and groaning. She fainted twice after waking in the morning. The patient visited a neurology clinic and underwent brain MRI, but the underlying cause remained unknown. At the age of 21, she experienced dizziness while walking or trying to get up in the morning. She experienced syncope and visited a hospital, where automated ECG diagnosis was within the normal range (Figures 3A, 3B). Brain computed tomography and electroencephalogram revealed no obvious abnormality. Therefore, the physician found no apparent cause for her syncope and she returned her home. The patient continued to have episodes of syncope several times a year until she the age of 27. Throughout this period, she visited several hospitals and clinics. However, episodes of syncope due to long QT syndrome was not suspected, and the patient did not undergo another ECG examination nor was referred to a cardiologist. After admission to our hospital, the ECG recorded at the age of 21 was retrieved and re-evaluated. Her ECG revealed QT prolongation with notched T waves (Figure 3A), a finding that was clearly abnormal (QT/QTc, 580/608 ms). Genetic analysis for long QT syndrome including KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 was performed after obtaining written informed consent from the patient. A novel frameshift variant that resulted from duplication (c. 526dupC, p.R176fsX331) in KCNH2 was identified (Figure 2B). Her mother and son, who did not have QT prolongation, did not carry the variant (Figure 2A). The patient was diagnosed with type 2 long QT syndrome. Carvedilol was initiated from 5.0 mg per day, and the dose was gradually increased. One month later, her QT interval had shortened (QT/QTc, 480/488 ms), and notched T waves had disappeared (Figure 4A). Two months later, when taking 7.5 mg carvedilol per day, her QT interval shortened further (QT/QTc, 460/460 ms) (Figure 4B). After six months of receiving 10 mg carvedilol per day, her QT interval completely normalized (QT/QTc, 450/442), and T-wave shape was no longer abnormal (Figure 4C). The patient recovered well, and no syncope recurrence was observed throughout a 3-year follow-up period.

Figure 1. A) Twelve-lead electrocardiogram on admission. B) Tracings of bedside continuous single-lead ECG after admission. Torsades de pointes spontaneously occurred with typical initiating the “short-long-short” sequence.
Figure 2. A) Pedigree of KCNH2, p.R176fsX331. Circles and squares indicate females and males, respectively. Closed symbol indicates a history of syncope. Plus signs indicate variant positive subjects, whereas minus signs indicate variant negative subjects. The black arrow indicates the proband of the family. Electrocardiograms in lead V5 of the patient’s mother and son showed no QT prolongation. B) Electropherograms of KCNH2 in control and the KCNH2 gene variant, p.R176fsX331(c.526dupC), in the patient.

Figure 3. A) Twelve-lead electrocardiogram (ECG) recorded when the patient was aged 21 years. B) An automated diagnosis based on ECG.
evaluate data carefully. Instead, the the previous study revealed that automated ECG diagnosis concluded [5,6], and measurement differences between algorithms in the degradation is underestimated or unreported via diagnostic software ECG diagnoses are not always correct. In particular, QT prolonged ECG diagnoses are widely utilized in medical practices with physicians to immediately use findings in the clinic. The automat it reduces the effort needed to evaluate ECG findings and allows crucial [2]. Moreover, patients with cardiac syncope have the highest risk of recurrence and are at increased risk of death from any cause related to syncope [1]. ECG facilitates the diagnosis of cardiac syncope and improves the prognosis of patients. Therefore, to ensure an accurate diagnosis and determine the cause of syncope, multiple ECG examinations and careful analysis of results are crucial [2]. Automated ECG diagnosis benefits physicians because it reduces the effort needed to evaluate ECG findings and allows physicians to immediately use findings in the clinic. The automated ECG diagnoses are widely utilized in medical practices with non-expert physicians and medical staff [4]. However, automated ECG diagnoses are not always correct. In particular, QT prolongation is underestimated or unreported via diagnostic software [5,6], and measurement differences between algorithms in the determination of QT interval are larger in patients with congenital [7,8] and acquired [9] long QT interval than in healthy subjects. A previous study revealed that automated ECG diagnosis concluded that findings were “normal” in 42.1% of patients with a prolonged QTc interval [6]. The phenomenon was observed for algorithms of various manufacturers [10]. From these perspectives, automated ECG diagnosis plus over-reading by physicians offer the accurate diagnosis, and long QT syndrome experts strongly advocate manual measurement [5,11,12]. In the present case, apparent and obvious QT prolongation at 21 years of age (Figure 3A) was missed due to an incorrect automated ECG diagnosis. T waves in leads I, II, III, aVR, aVF, and V2-V6 had prominent notches, and the second component of the T wave should have been included in the analysis of the QT interval [11]. The automated ECG diagnosis did not consider the second component of the notched T wave, and instead regarded the endpoint of the first component of the notched T wave as the endpoint of the QT interval. If the physician had self-evaluated ECG findings, they would have noticed the markedly prolonged QT interval and bimodal T waves, even if the QT interval was inaccurately measured. The patient was administered carvedilol, a non-selective β- and α1-blocker, from the age of 27, when she was diagnosed with type 2 long QT syndrome. In a prior report, we showed that carvedilol may be used to effectively treat type 2 long QT syndrome [14]. It was suggested that α1-adrenergic stimulation acutely reduces Kv 11.1 channel activity via the membrane PIP2 pathway [15]. Acute α1-adrenoceptor-mediated reduction in I_K at lower heart rate would act additionally to prolong action potential durations and may enhance inward current through Na/Ca exchanger. After the administration of carvedilol, the patient had no episodes of syncope and her QT interval at rest shortened considerably.

6. Conclusions
ECG is an essential method that may be used in the examination of
patients with recurrent syncope. Moreover, all physicians should confirm ECG with their own eyes if there is QT prolongation and not rely exclusively on automated ECG diagnosis.

References