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【 CASE REPORT 】

Successful Management of a Young Athlete with Type 2 Long QT Syndrome by Genotype-specific Risk Stratification and Bridging Therapy with a Wearable Cardioverter Defibrillator

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Abstract:
We herein report a 14-year-old boy with repetitive nocturnal syncope related to medication-refractory long QT syndrome (LQTS). Although the use of an implantable cardioverter-defibrillator (ICD) was inevitable to prevent sudden cardiac death, he refused immediate implantation in order to play in a baseball competition six weeks away. Given his genetic diagnosis of type 2 LQTS, which is associated with cardiac events unrelated to exercise, we prescribed a wearable cardioverter defibrillator (WCD) to be donned at night, without limiting his exercise participation. An ICD was implanted after the competition. We successfully performed the preplanned treatment while maximizing the patient's quality-of-life with a WCD and genotype-specific risk stratification.

Key words: long QT syndrome, wearable cardioverter defibrillator, gene diagnosis, sports participation, quality of life

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Introduction

Congenital long QT syndrome (LQTS) is a genetic arrhythmogenic disorder that can cause life-threatening arrhythmia (1). Because of its characteristic correlation between genotype and phenotype, a genetic analysis of patients with LQTS is essential for confirming the diagnosis and providing gene-specific care. We encountered a patient with repetitive syncopal episodes related to medication-refractory LQTS whose risk of sudden cardiac death (SCD) was successfully managed in a genotype specific manner.

Bridging therapy with a wearable cardioverter defibrillator (WCD) also played an important role in minimizing the present patient's risk. WCDs are typically used for a limited period of time for patients in danger of suffering ventricular arrhythmias (e.g. the early phase of post-myocardial infarction) or those awaiting the implantation of an ICD (implantable cardioverter-defibrillator) but in temporary contraindication (e.g. infection). We therefore described another useful application of a WCD: for preventing nocturnal death in a young patient with an inherited arrhythmia syndrome.

We obtained written informed-consent from the patient and his family members to conduct this research plan, including the genetic analysis, which was approved by the ethics committee of Shiga University of Medical Science.

Case Report

A 14-year-old Japanese boy with repetitive episodes of syncope was referred to our hospital. He had been diagnosed with LQTS and treated with 150 mg mexiletine hydro chloride based on suspicion of type 3 LQTS (LQT3) without genetic screening. He had been suspected of having LQT3 because his prolonged QT interval on a resting electrocardiogram (ECG) was not further increased by exercise. However, he suffered from recurrent syncope several times before dawn. When he was introduced to our hospital, his

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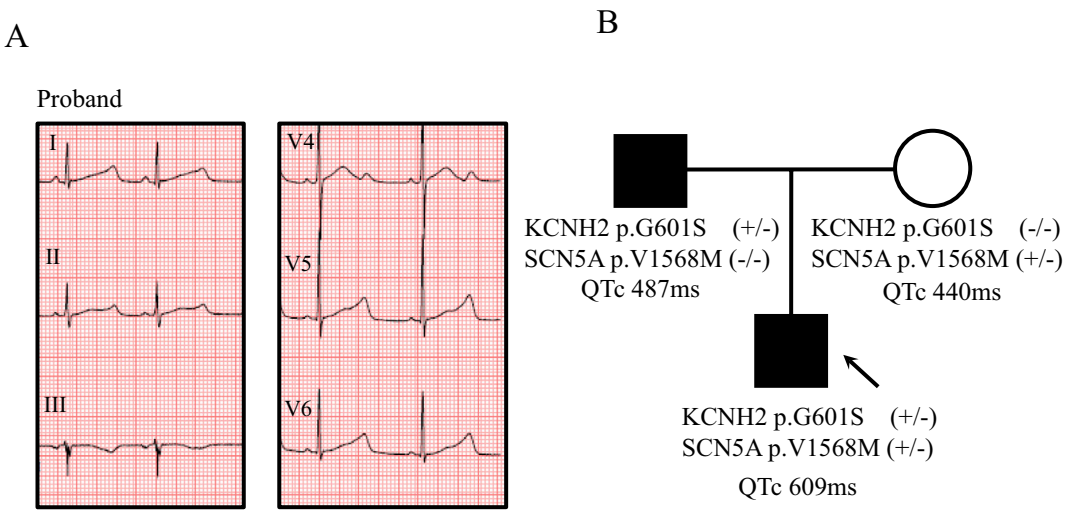

Figure 1. ECGs and the family pedigree. A: ECGs of the patient. At the first visit to our hospital, the patient's ECG showed a QTc of 609 ms. B: Family pedigree. *Filled symbols*: Family members with QT prolongation.

ECG showed a QTc of 609 ms without electrolyte abnormalities, even under mexiletine treatment (Fig. 1).

We performed a genetic analysis for known causative genes of LQTS (2), and the analysis identified *KCNH2* p.G601S (c.G1801A) and *SCN5A* p.V1568M (c.G4702A) (Fig. 2). *KCNH2* p.G601S is a reported pathogenic variant of LQT2 (3). This variant was also identified in the genomic DNA of the patient's father. The father's ECG also showed QTc prolongation, but he had never experienced syncope. The other variant, *SCN5A* p.V1568M, was inherited from the patient's mother. It was classified as a variant of unknown significance (VUS) in the American College of Medical Genetics and Genomics (ACMG) Guideline (4). In addition, the mother's QTc was in the normal range at 440 ms, and she had never experienced syncope. We therefore suspected that the patient had LQT2 but with a possible modifying variant in *SCN5A*.

Based on this genetic diagnosis, we administered oral bisoprolol fumarate (1.25 mg/day) to the patient. At the time, the nonselective beta blocker nadolol recommended by experts (5) was not readily available for in-hospital prescription. Mexiletine, started by the previous physician, was continued with an increased dose (450 mg/day) because it shortened the patient's QTc at the beginning and had been effective for quite some time. His ECG at 1 month post-discharge showed that the QTc had shortened to 465 ms without syncopal episodes. Bisoprolol fumarate was continued at the initial dose because his resting ECG showed bradycardia (40 bpm), considered at a maximum permissive dose. However, one month later, the patient was found unconscious in the early morning. He was successfully resuscitated by his parents with an automated external defibrillator (AED), and the VF was recorded (Fig. 2B).

When he arrived at the emergency department of our hospital, his ECG showed a prolonged QTc interval of 553 ms (Fig. 2C). He had never skipped his medication. The recurrence of syncopal episodes under medication suggested that ICD implantation was inevitable. However, the patient and his family rejected immediate implantation because the patient wished to participate in a baseball competition six weeks in the future.

Because the patient had never experienced syncope or cardiac arrest except in the early morning, and his genetic diagnosis was not LQT1, the risk of events during exercise was considered to be very low, and no exercise restrictions were indicated. Nevertheless, the risk of nocturnal arrhythmia had to be managed properly. We therefore decided to provide the patient with a WCD only while he slept alongside nadolol administration (30 mg/day) to postpone the ICD implantation, thereby allowing him to play in the competition. During the six weeks of follow-up, we observed no cardiac events. After the patient's competition ended, we implanted an ICD as planned.

Discussion

In this report, we presented a patient with medication refractory LQTS who had been suspected of having LQT3 in the past but was ultimately revealed to have LQT2. Without a genetic analysis, making a correct diagnosis of LQTS genotype can be difficult, and an inappropriate medication choice can lead to serious consequences. A genetic analysis to ensure correct LQTS genotyping is the current standard and an indispensable diagnostic process.

This report also sheds light on the benefit of LQTS genotyping for young individuals who regularly participate in sports, in order to avoid unnecessary exercise limitations. More than 17 genes have been associated with LQTS to date (2, 6), and variants in several genes are known to cause distinct phenotypes. Among them, LQT1, LQT2, and LQT3 account for 70% of genotyped cases. Schwartz et al. (7) reported that life-threatening arrhythmia related to exercise is

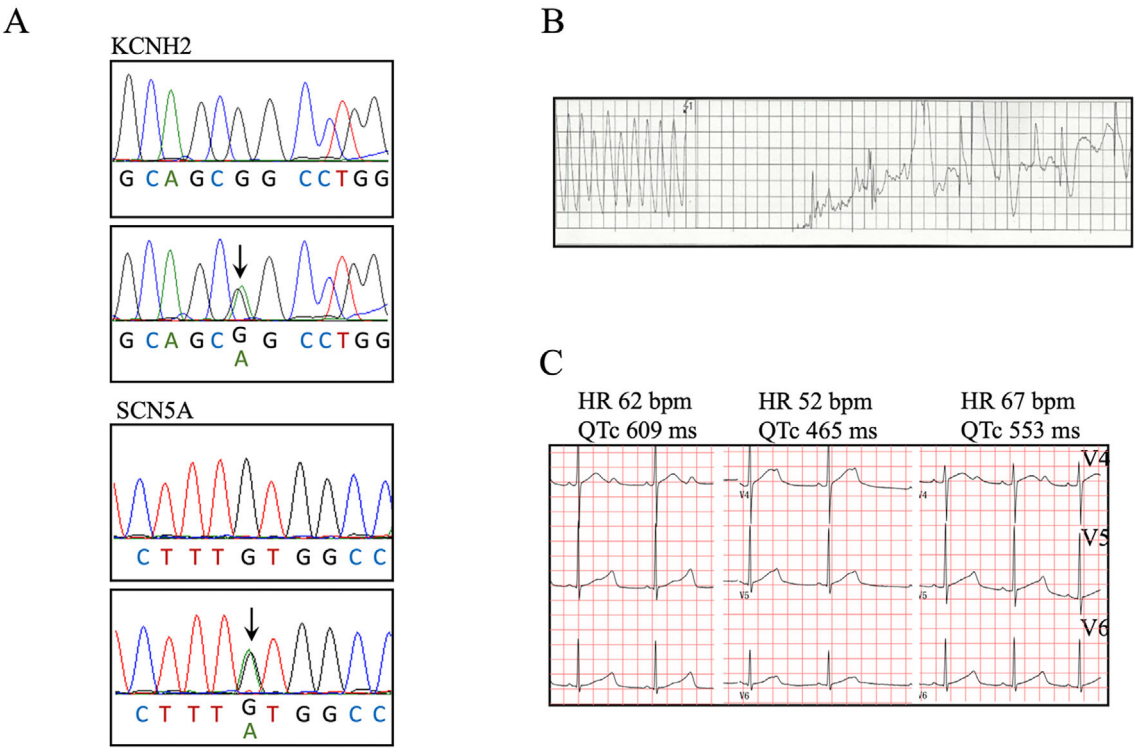

Figure 2. **A genetic analysis and ECG records. A: Upper two panels: the genetic sequences of *KCNH2* from a healthy control sample and the proband. Arrow: G to A substitution at position 1801 (c.1801 G>A). Lower two panels: the genetic sequences of *SCN5A*. The proband's sequence has a G to A substitution at site 4702 (c. 4702 G>A). B: a VF event recorded by an AED. C: time course of QTc duration. From left to right, an ECG before beta-blocker administration (HR 62 bpm, QTc 609 ms); under beta-blocker and mexiletine therapy (HR 52 bpm, QTc 465 ms); and after VF attack occurred even under medication (HR 67 bpm, QTc 553 ms).**

observed mostly in LQT1 patients and has never been reported to occur in LQT2 patients. In contrast, 49% of lethal cardiac events occurred during sleep or at rest in LQT2 patients. In addition, symptomatic LQT2 patients are at a high risk of recurrent cardiac events later in life, and 65% of symptomatic patients tend to experience a cardiac event under conditions that are similar to those of their first event (7). Based on these findings, the current scientific statement from the American Heart Association and the American College of Cardiology is relatively generous regarding sports participation for certain types of LQTS (8). The time after breakthrough cardiac events until patients can return to exercise remains controversial. The statement recommends restricting participation in competitive sporting events for three months. However, supporting evidence is poor at present. In addition, the exercise stress of playing baseball is only around 4 to 5 metabolic equivalents (METS), which is classified as moderate. We took these points into consideration and did not prescribe sports limitation for the patient.

This case also highlights the usefulness of nighttime bridging therapy with a WCD for LQT2 and LQT3 patients for whom immediate ICD implantation needs to be postponed for whatever reason. The use of a WCD may be indicated for patients at a temporary risk of ventricular arrhythmias, such as during the early phase after myocardial infarction or myocarditis, or for those at high risk of sudden death but who need to defer immediate implantation for certain medical conditions. The effectiveness of a WCD in preventing SCD is reported to be comparable to that of a traditional ICD (9). LQTS patients are at risk of experiencing SCD not temporarily but throughout their lifetimes, and they are thus not generally likely to be WCD candidates. However, in some circumstances (such as those described herein), a WCD can be a useful tool for risk management. A review of multiple cases also reported the usefulness of WCD in LQTS patients who are at temporarily increased risk of SCD (10). Physicians should consider this device as a possible tool for SCD risk reduction. Regarding the wearing time, its use should also be considered during the daytime, not just at night, depending on the severity of a given case, as arrhythmic events can be induced by auditory and emotional stimuli in LQT2 cases.

To maximize the efficacy of a WCD and also avoid inappropriate shocks, it is necessary to understand the characteristics of each patient's ventricular arrhythmias, including the triggers, environmental factors, and high-risk periods. A genetic analysis is an indispensable tool for this purpose and should be considered for all patients with LQTS.

The authors state that they have no Conflict of Interest (COI).

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