Long QT Syndrome with Nocturnal Cardiac Events Caused by a *KCNH2* Missense Mutation (G604S)

Akinori Sato¹, Masaomi Chinushi², Hiroshi Suzuki³, Fujito Numano³, Takanori Hanyu³,
Kenichi Iijima¹, Hiroshi Watanabe¹ and Hiroshi Furushima¹

Abstract

An 8-year-old boy suffered from an unconsciousness attack and torsade de pointes arrhythmia during sleep or at rest. His electrocardiogram showed prolonged QT intervals, but the T wave morphology was atypical for type 1, 2 or 3 congenital long-QT syndrome (LQTS). Intravenous epinephrine slightly prolonged the QT interval whereas mexiletine infusion shortened the QT interval. Although these clinical characteristics might suggest type 3 LQTS, a genetic analysis identified the G604S-*KCNH2* mutation (type 2 LQTS). Because mismatches between the genotype and phenotype of LQTS are possible, genetic analysis of LQTS is important to identify the most appropriate therapeutic option and risk stratification.

Key words: Long QT syndrome, Torsade de pointes, *KCNH2* gene

(Intern Med 51: 1857-1860, 2012)

(DOI: 10.2169/internalmedicine.51.7494)

Introduction

Long QT syndrome (LQTS) is a hereditary disorder characterized by prolongation of the QT interval on electrocardiogram (ECG), syncope, and sudden death due to torsade de pointes (TdP) and/or ventricular fibrillation (1). To date, thirteen genes have been reported as LQTS-causing genes, and most mutations identified in LQTS patients are in the *KCNQ1*, *KCNH2*, and *SCN5A* genes, which correspond to types 1, 2, and 3 LQTS (LQT1, LQT2, and LQT3), respectively (2-4). Identification of the LQTS genotype is important especially in patients suffering from cardiac events. This is because selection and effects of the pharmacological treatment, caution and regulation during daytime activity, and/or indication of non-pharmacological treatment (pacemaker or implantable cardioverter defibrillator) are different depending on the genotype of LQTS. Although previous studies reported specific correlations between genotype and phenotype (configuration of the QT interval prolongation, circumstances and triggers of cardiac events, effect of the pharmacological drug, etc) in LQT1, LQT2 and LQT3, these clinical characteristics do not always fully predict (or identify)

the genotype of LQTS (5-8).

Here, we present an 8-year-old boy with LQTS who has had episodes of TdP during nocturnal period or at rest. Both the circumstance of the cardiac events and effects of the pharmacological agents (epinephrine and mexiletine) to the QT/QTc interval seemed partially compatible to a LQT3 genotype, but genetic analysis revealed a mutation in the *KCNH2* gene (LQT2).

Case Report

The initial reported symptom occurred while quietly reading a book in the evening, when the 8-year-old boy lost consciousness. Systemic rigidity and rolling back of the eyes were confirmed by his father, and his consciousness spontaneously restored 10 minutes later. At the emergent outpatient clinic, his neurological findings, hematological and serological tests were all normal. His heart rate was 69 bpm, and a prolonged QT/QTc interval (490/526 ms) and a notched T-wave in the V₄ lead and late peaked T in leads II, III, aV_F and V₅-V₆ were confirmed on his ECG (Fig. 1A). The next day, self-terminating TdP was recorded on Holter ECG (Fig. 1B). The TdP developed during his sleeping early

---

¹Division of Cardiology, Niigata University Graduate School of Medical and Dental Sciences, Japan, ²School of Health Sciences, Niigata University, Japan and ³Department of Pediatrics, Niigata University Medical and Dental Hospital, Japan

Received for publication February 7, 2012; Accepted for publication April 15, 2012

Correspondence to Dr. Masaomi Chinushi, masaomi@clg.niigata-u.ac.jp

Figure 1. Twelve-lead electrocardiogram (ECG) of the proband showed a prolonged QT/QTc interval (490/526 ms), and a notched T wave in the V₄ lead and late peaked T in leads II, III, aV_F and V₅-V₆ (A). Ambulatory ECG demonstrated an episode of torsade de pointes (Tdp) during sleep. Heart rate acceleration due to sinus tachycardia was associated with the initiation of Tdp (B). Intravenous administration of epinephrine showed small effect on the QTc interval (C) whereas mexiletine infusion shortened the QTc interval (D).

in the morning, and transient heart rate acceleration due to sinus tachycardia (from 51 to 125 bpm) was preceded by Tdp initiation without having premature beats or a short-long-short cardiac cycle. His father declared that the boy had been sleeping well, and no loud sound was present around that time. LQTS was the most likely diagnosis as a cause of the Tdp and his syncope episodes.

The boy was referred to our hospital for further study and treatment. His family had no history of sudden cardiac death or syncope. His mother's ECG also showed a mildly prolonged QTc interval but the T wave configuration was not typical for any genotypes of LQTS patients (Fig. 2A). The QT/QTc interval of his father and sister were in the normal range (Fig. 2B). Intravenous administration of epinephrine (0.1 µg/kg bolus infusion followed by 0.1 µg/kg/min maintenance administration for 5 minutes) induced a small degree of QT/QTc interval prolongation [530/564 ms at the baseline (68 bpm), 530/608 ms at the peak heart rate (79 bpm), and 540/587 ms at the steady state (71 bpm)] (Fig. 1C). Neither T-wave morphological change nor ventricular tachyarrhythmias were observed during the test. On the other hand, intravenous administration of mexiletine (2.0 mg/kg) shortened the QT/QTc interval from 520/581 to 460/521 ms (-11.5%/-10.3%) without change of the heart rate (75 vs. 77 bpm) (Fig. 1D). Mexiletine also shortened Q-T(peak) interval and T(peak)-T(end) interval from 435 to 385 ms

(-11.5%) and from 85 to 75 ms (-11.8%), respectively. Pharmacological treatment with propranolol (25 mg/day), mexiletine (300 mg/day) and potassium L-aspartate (1,800 mg/day) were administered. During the treatment, serum potassium was controlled at 3.9-4.0 mEq/L, and neither marked bradycardia (less than 45 bpm) nor ventricular tachyarrhythmias were observed in his ECG monitoring. Treadmill exercise test did not induce ventricular tachyarrhythmia, and QT/QTc intervals were 440/468 ms at the baseline, 380/510 ms at the first stage of Bruce protocol, and 280/498 ms at maximum exercise.

His parents did not agree to the treatment of an implantable cardioverter-defibrillator (ICD) primarily because of the small body size of the patient (BW 25 kg, height 126 cm). They have learned basic life support techniques, and an automated external defibrillator (AED) has been placed at his house. Neither syncope attack nor any cardiac events recurred during a 10-month follow-up period. After obtaining informed consent, a genetic analysis of cardiac ion channel genes was performed. Report of this study was completed after his discharge from our hospital. The proband had a heterozygous *KCNH2* missense mutation (G604S) (Fig. 2C) without showing other mutations in the other LQT-causing genes (*KCNQ1*, *SCN5A*, *KCNE1*, or *KCNE2*). This patient was diagnosed as LQT2.

Figure 2. Twelve-lead electrocardiogram (ECG) of the proband's mother showed a mildly prolonged QTc interval (455 ms) but the T wave configuration was normal (A). Pedigree of a patient with long QT syndrome (LQTS) carrying the *KCNH2* mutation. The white squares and white circles represent asymptomatic males and females respectively, and the black square and arrow indicate the proband. The QT/corrected QT interval (QTc) of the asymptomatic males and females were within the normal range, but not in the proband (B). y/o: years old, Tdp: torsade de pointes. Mutation analysis of the proband. Sequencing data showed a missense mutation of G1810A in the *KCNH2* gene, causing a substitution from glycine in the 604th amino acid to serine (G604S) (C).

Discussion

Previous studies suggested the specific correlation between genotype and phenotypes in patients with LQT1, LQT2 or LQT3 (1). Specific T-wave morphologies were reported in each genotype of LQTS; broad-based prolonged T waves in LQT1, low-amplitude or notched T waves in LQT2, and late-appearing T waves in LQT3 (5, 6). Twelve-lead ECG in the present patient showed a notched T wave in lead V4 and a late peaked T wave in leads II, III, aV_F and V₅-V₆. Therefore, we consider that this patient's ECG is not typical for any genotype of LQTS although LQT2 might be the most likely genotype based on his ECG configuration (5, 6).

Different triggers and/or circumstance for the cardiac events were reported in each genotype of LQTS; cardiac events frequently occurred during sympathetic stimulation in LQT1, by emotional stress and/or by sudden auditory stimulation such as telephone rings and/or alarm clocks in LQT2, and during rest/sleep without arousal in LQT3 (7, 8). Since cardiac events of this patient occurred at rest or during sleep without auditory stimulus, the circumstance of the cardiac events seemed to suggest LQT3 as a genotype of this patient. Although his cardiac events occurred during sleep or

at rest, the initial pattern of Tdp recorded in the Holter ECG (heart rate acceleration and non-pause dependence) might suggest that LQT1 was a possible genotype of this patient (8).

A previous study by Shimizu et al. demonstrated that bolus injection and/or continuous infusion of epinephrine induced QTc interval prolongation in LQT1 (+27% at peak effect and +17% during steady state effect) and in LQT2 (+25% at peak effect and +3% during steady state effect) (9). On the other hand, QTc interval in LQT3 patients was mostly stable or shortened during epinephrine infusion (+7% at peak effect and -2% during steady state effect) (9). According to that study, we think that the results of the epinephrine test might suggest LQT3 as a likely genotype of the current patient. This is because the magnitude of the epinephrine-induced QTc interval prolongation as compared to the baseline level was mild at the peak effect (+44 ms, +8%) and steady state effect (+23 ms, +4%) of epinephrine infusion in this patient.

Furthermore, Schwartz et al. reported that mexiletine shortened QTc interval markedly in LQT3 patients (-17%), but only mildly in LQT2 (-5%) (10). In the present patient, the magnitude of the QTc interval shortening was 60 ms (-10%), and this value may be small for a LQT3 patient but large for a LQT2 patient according to their report.

Treadmill exercise test did not induce ventricular tachyarrhythmia, and QTc intervals were moderately prolonged (QT/QTc 440/468 ms at the baseline, 380/510 ms at the first stage of Bruce protocol, and 280/498 ms at maximum exercise). The QT/QTc interval response during the treadmill test was atypical of LQT3 genotype but it was not fully typical of LQT2 patients either (the slight QTc interval prolongation by exercise) according to the previous study by Hekkala et al. (11).

Nevertheless, the present patient was finally diagnosed as LQT2 based on the result of genetic analysis. Indeed, several studies reported that about 30% of the cardiac events in LQT2 patients occurred during sleep or at rest (7). Therefore, it is important that the heart rate acceleration, which was most likely due to sympathetic nerve stimulation, preceded the Tdp in this patient. Previous studies demonstrated that heart rate increases during rapid eye movement (REM) sleep because of transient augmentation of sympathetic nerve activity during the period (12). However, it is still unknown how the circadian change of autonomic nerve activity during sleep plays an arrhythmogenic role in the initiation of Tdp in LQT2 patients.

In this patient, the genetic analysis identified a missense mutation (G604S) in the *KCNH2* gene. The *KCNH2* gene encodes the α -subunit of the rapidly activating delayed rectifier potassium ion channel, which provides I_{Kr} for repolarization of the cardiac action potential. This mutation has been studied in a Chinese family of 36 members. When genetic analysis was performed in this family, sudden cardiac death during sleep had already been reported in 4 of the family members. All 10 family members carrying the G604S-*KCNH2* mutation showed QT interval prolongation, and interestingly, 7 of the 10 carriers had syncopal episodes during rest/sleep (13). Therefore, the clinical characteristics of a patient with the G604S-*KCNH2* mutation showed high penetrance for QT prolongation and syncope or sudden death episodes during sleep/rest. Huo et al. experimentally characterized the pathophysiological consequences of the G604S-*KCNH2* mutation at the cellular level (14). The G604S-*KCNH2* mutant channel did not produce any currents by itself and exhibited dominant-negative current suppression with the wild type *KCNH2* α -subunits, which is caused by a trafficking defect and altered channel-gating properties. However, the mechanism connecting the impaired *KCNH2* channel with nocturnal attacks remains unknown.

Although it has been previously reported that the genotype and phenotype correlation in LQTS is useful to predict the genotype and to select the initial treatment, clinical characteristics in some mutation of LQTS (like a *KCNH2* mutation in the present patient) may be atypical (8). Therefore, genetic analysis of LQTS is important to identify the therapeutic option and risk stratification (15). In the current patient, additional treatment with ICD was not performed be-

cause (i) a less invasive transvenous implantation approach was already inapplicable in his small body size and (ii) beta-blocker and supplemental treatment of potassium are thought to be effective in most LQT2 patients (16). Although his clinical course after discharge has been non-eventful, careful follow-up is required because another cardiac event can recur during sleep.

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

References

1. Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* **51**: 2291-2300, 2008.
2. Wang Q, Curran ME, Splawski I, et al. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. *Nat Genet* **12**: 17-23, 1996.
3. Curran ME, Splawski I, Timothy KW, Vincent GM, Green ED, Keating MT. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. *Cell* **80**: 795-803, 1995.
4. Wang Q, Shen J, Splawski I, et al. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. *Cell* **80**: 805-811, 1995.
5. Moss AJ, Zareba W, Benhorin J, et al. ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. *Circulation* **92**: 2929-2934, 1995.
6. Zhang L, Timothy KW, Vincent GM, et al. Spectrum of ST-T-wave patterns and repolarization parameters in congenital long-QT syndrome: ECG findings identify genotypes. *Circulation* **102**: 2849-2855, 2000.
7. Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* **103**: 89-95, 2001.
8. Tan HL, Bardai A, Shimizu W, et al. Genotype-specific onset of arrhythmias in congenital long-QT syndrome: possible therapy implications. *Circulation* **114**: 2096-2103, 2006.
9. Shimizu W, Noda T, Takaki H, et al. Diagnostic value of epinephrine test for genotyping LQT1, LQT2, and LQT3 forms of congenital long QT syndrome. *Heart Rhythm* **1**: 276-283, 2004.
10. Schwartz PJ, Priori SG, Locati EH, et al. Long QT syndrome patients with mutations of the SCN5A and HERG genes have differential responses to Na⁺ channel blockade and to increases in heart rate. Implications for gene-specific therapy. *Circulation* **92**: 3381-3386, 1995.
11. Hekkala AM, Viitasalo M, Vaananen H, Swan H, Toivonen L. Abnormal repolarization dynamics revealed in exercise test in long QT syndrome mutation carriers with normal resting QT interval. *Europace* **12**: 1296-1301, 2010.
12. Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic nerve activity during sleep in normal subjects. *N Engl J Med* **328**: 303-307, 1993.
13. Zhang Y, Zhou N, Jiang W, et al. A missense mutation (G604S) in the S5/pore region of HERG causes long QT syndrome in a Chinese family with a high incidence of sudden unexpected death. *Eur J Pediatr* **166**: 927-933, 2007.
14. Huo J, Zhang Y, Huang N, et al. The G604S-HERG mutation alters the biophysical properties and exerts a dominant-negative effect on expression of hERG channels in HEK293 cells. *Pflugers Arch* **456**: 917-928, 2008.
15. Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. *N Engl J Med* **348**: 1866-1874, 2003.
16. Etheridge SP, Compton SJ, Tristani-Firouzi M, Mason JW. A new oral therapy for long QT syndrome: long-term oral potassium improves repolarization in patients with HERG mutations. *J Am Coll Cardiol* **42**: 1777-1782, 2003.