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Abnormal repolarization dynamics in a patient with *KCNE1(G38S)* who presented with torsades de pointes☆,☆☆,★

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Abstract Risk of G38S, major *KCNE1* polymorphism [*KCNE1(G38S)*], for long QT syndrome (LQTS) remains unclear. A 72-year-old woman was admitted with recurrent torsades de pointes (TdP). She had remarkable QT prolongation (corrected QT interval 568 ms) under conditions of hypokalemia and hypomagnesemia. After correction of this electrolytic imbalance, TdP was suppressed and metoprolol was started. The QT-RR slope in 24-hour Holter electrocardiogram was steep and this enhanced bradycardia-dependent QT prolongation was similar to that in LQTS. She carried *KCNE1(G38S)*. Patients with *KCNE1(G38S)* could have similar potential risk of ventricular arrhythmia as with LQTS. Analysis of QT-RR relationship could also evaluate the latent arrhythmogenicity of *KCNE1(G38S)*.

Keywords: QT-RR relation; *KCNE1(G38S)*; long QT syndrome; hypokalemia; hypomagnesemia

Introduction

KCNE1 (*minK*, *IsK*) encodes the subunit that serves a modulator of *KCNH2* (human ether-à-go-go-related gene, $K_V11.1$) and KCNQ1 (K_VLQT1, $K_V7.1$) channels. KCNH2 and KCNQ1 channels mediate the rapid and slow delayed rectifier K^+ currents, i.e., I_{Kr} and I_{Ks}, respectively. There is a common single-nucleotide polymorphism (SNP) between guanine and adenine at base position 112 of *KCNE1*. This SNP results in a *KCNE1* subunit variant with glycine at amino acid position 38 [*KCNE1(S38G)* subunit] and a variant with serine at the same position [*KCNE1(G38S)* subunit]. *KCNE1(G38S)* carriers share the minor part of the population in most of the ethnic groups examined so far [1], indicating that inheritance of *KCNE1(G38S)* may give a disadvantage in survival. Nevertheless, the contribution of *KCNE1(G38S)* to risk for long QT syndrome (LQTS) remains unclear. Previous studies reported conflicting results; normal QT intervals [2] and prolonged QT intervals [3] in *KCNE1(G38S)* carriers.

The conventional QT interval measurement using 12-lead electrocardiogram (ECG) has a limited ability to detect LQTS because it yields a QT interval only at a certain heart rate [4]. The QT-RR relationship, which indicates rate-dependent QT dynamics, is a useful tool to detect QT prolongation during bradycardia in LQT2 as well as LQT1 patients [5–8]. Herein, we report a case of an elderly *KCNE1(G38S)* carrier patient who admitted with recurrent torsades de pointes (TdP). We successfully assessed abnormal rate-dependent QT dynamics and effects of beta-blocker by evaluation of the QT-RR relationship. Analysis of QT-RR relationship could also have a potential for evaluating the latent arrhythmogenicity of *KCNE1(G38S)*.

Case report

A 74-year-old woman with atrial fibrillation (AF) and a history of mitral valve repair was admitted to our hospital for treatment of frequent TdP. She had been taking furosemide 20 mg/day, warfarin 2 mg/day and fexofenadine 120 mg/day for her clinical condition. Although she had never taken QT prolonging drugs, she sometimes presented with recurrent episodes of palpitation and presyncope. In the Holter ECG at her family doctor's clinic, QT interval was prolonged and TdP

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with presyncope was frequently observed (Fig. 1). On admission, blood pressure was 104/74 mm Hg and heart rate was 77 beats/min. Laboratory data indicated hypokalemia (3.1 mEq/l) and hypomagnesemia (1.6 mg/dl). A 12-lead ECG demonstrated atrial fibrillation and remarkable QT prolongation. The five-beat averaged QT interval calculated using Bazett's formula [corrected QT interval (QTc)] was 568 ms in V_4 lead with notched T-wave (Fig. 2A). Accuracy of measurement of QT interval was confirmed by two experienced investigators who were blind to the clinical information of the patient. Although hypokalemia and hypomagnesemia were corrected (4.5 mEq/l and 2.1 mg/dl, respectively) and TdP was suppressed, QT prolongation was not significantly improved (QTc = 548 ms in V_4 lead). QT prolongation was significantly corrected (QTc = 492 ms in V_4 lead) after metoprolol (20 mg/day) was started.

We analyzed QT-RR relations using the Holter ECG analyzing system SCM-6000 (Fukuda Denshi, Tokyo, Japan) and evaluated rate-dependent QT dynamics [9]. To assess QT-RR relationship, QT interval of each single beat was plotted against the previous RR interval. The QT-RR slope on admission was steep and this enhanced bradycardia-dependent QT prolongation was similar to that in LQTS, especially LQT2 [10] (Fig. 3A). The QT-RR slope was decreased after treatment of hypokalemia and hypomagnesemia (Fig. 3B), and furthermore after metoprolol (20 mg/day) was started (Fig. 3C).

From the analysis of QT-RR relationship, she potentially had acquired LQTS; therefore, she underwent genetic testing. She carried only the *KCNE1(G38S)* and not any other amino acid changes in the major cardiac ion channels (Table 1). After starting metoprolol (20 mg/day), palpitation and presyncopal episodes have never recurred.

Discussion

This case report suggested that *KCNE1(G38S)* could lead to a potential risk for abnormal QT prolongation and occurrence of TdP when QT prolonging factors were present.

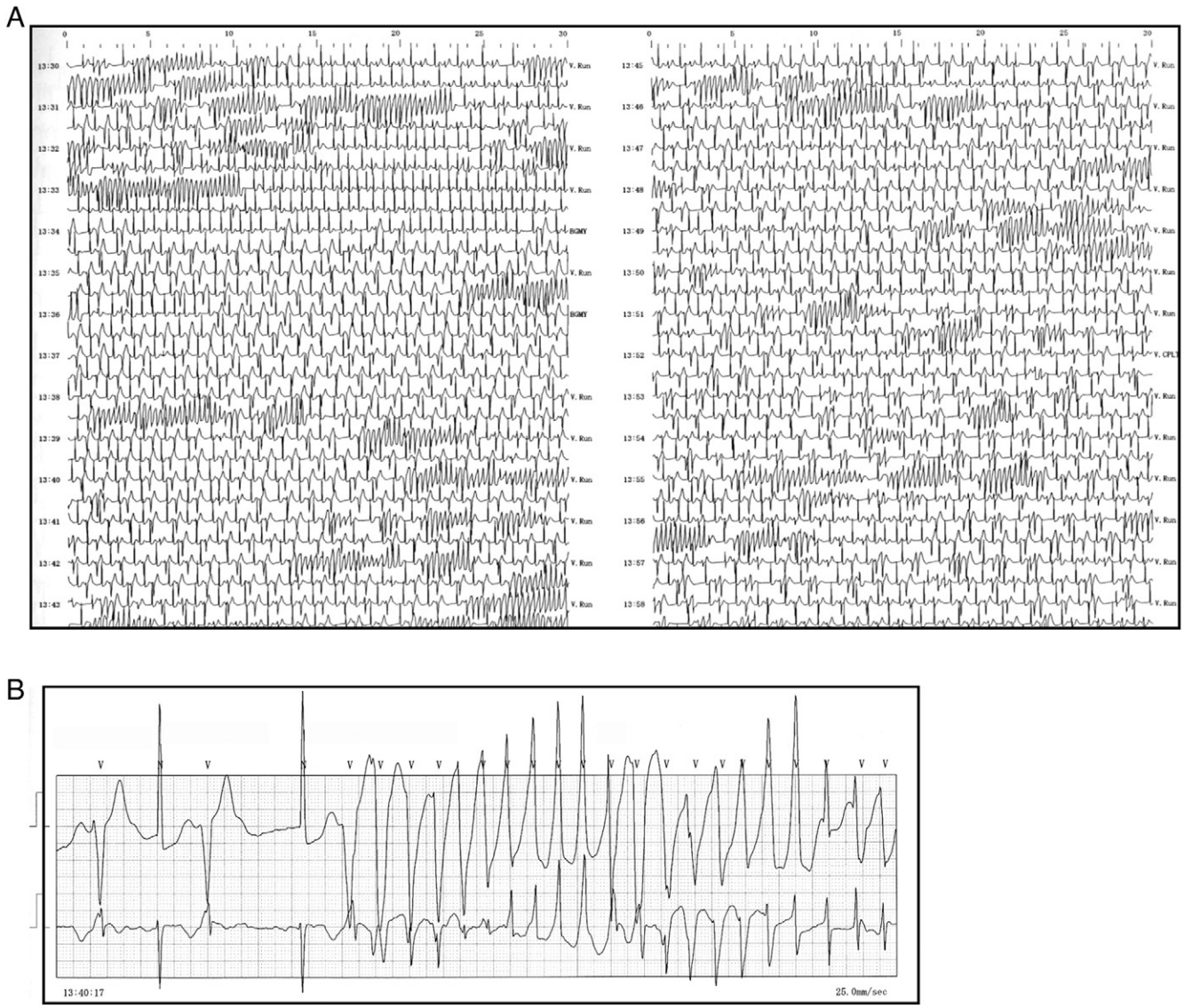

Fig. 1. Torsades de pointes with presyncope incessantly occurred in the 24 hour Holter ECG recorded at her family doctor's clinic (Panel A). It was induced after short-long-short sequence caused by ventricular bigeminy (Panel B).