To the Editor: The acquired form of long QT syndrome (LQTS) is often induced by hypokalemia or drugs. Hypokalemia and drugs cause QT prolongation via reduction in the rapidly activating component of the delayed rectifier K\textsuperscript+ currents (I\textsubscript{Kr}). Therefore, the KCNH2 (HERG) channel conducting I\textsubscript{Kr} is recognized as the most susceptible channel in acquired LQTS. However, the autoimmune effect on the KCNH2 channel has not been elucidated.

In the present report, we describe a female patient with an acquired form of LQTS with no known cause of QT prolongation. We used the patch clamp method (1) to determine whether her serum and immunoglobulin (Ig)G reduced I\textsubscript{Kr}, and we performed Western blot analysis to determine whether her IgG included anti-KCNH2 antibodies.

The patient was a 42-year-old female who had a normal clinical history until recurrent episodes of syncope for 3 months. An electrocardiogram (ECG) showed marked QT prolongation, T-wave alternans, and episodes of Torsades de pointes (Fig. 1A). Treatment with atrial pacing (70/min) and intravenous magnesium infusion were started, but the corrected QT interval (QTc) was persistently prolonged (0.70 s ± 0.5) (Fig. 1B). The ECGs obtained at annual checkups for the previous 4 years were normal or at most borderline (0.45 to 0.46 for women), but with normal T-wave morphology and not suggestive of LQTS (QTc 0.43 s ± 0.5) (Fig. 1C), and there was no family history of QT prolongation or cardiac sudden death. The patient was not taking any drugs, and there was no evidence of structural heart disease or cerebrovascular disease. Laboratory data, including serum electrolytes and hormones, were normal except for detection of increased IgG concentration (1,783 mg/dl) and positive anti-Sjögren’s syndrome A (SSA)/Ro antibodies (141.3 index). The recurrence of syncope was diminished by oral administration of atenolol (100 mg/day) and verapamil (120 mg/day). The patient was discharged after implantation of an implantable cardioverter-defibrillator with pacing mode DDI (lower: 70/min). Prolonged QT interval and increased IgG level have remained, but ventricular tachycardia or fibrillation events have not been detected.

We screened for known LQTS-associated genes by polymerase chain reaction DNA conformation polymorphism analysis and DNA sequencing. We suspected LQT2 because of low-amplitude T waves in the ECG, but there was no mutation in the KCNH2 gene. Furthermore, no mutation was detected in KCNQ1, SCN5A, KCNE1, KCNE2, and KCNJ2 genes. There was a polymorphism (D85N) in KCNE1, which is heterozygously found in 2% of the Japanese population. Because ECGs for the previous 4 years were normal, D85N-KCNE1 may have not a causative but rather a modifying role in this LQTS patient.

The KCNH2 current stably expressed in HEK 293 cells was significantly reduced when cells had been cultured for 1 to 5 days in a medium to which 2% serum from the patient (Figs. 2A and 2D) or IgG (75 μg/ml) (Figs. 2B to 2D) had been added. When cells expressing KCNH2 that had been cultured in the patient’s serum were returned to the medium without serum overnight, the amplitudes of both KCNH2 outward and tail currents recovered to untreated levels. The patient’s serum had no effect on the slowly activating components of the delayed rectifier K\textsuperscript+ currents (I\textsubscript{Kr}) of HEK 293 cells expressing KCNQ1/KCNE1 (data not shown). Next, we tested whether the patient’s serum has an acute effect on KCNH2 currents (I). Direct application of 2% serum from the patient to physiologic solution for 5 min had no effect on either I\textsubscript{step} or I\textsubscript{tail}. These findings suggest that the patient’s IgG decreased KCNH2 expression. The mechanism is not clear, but endocytosis may be facilitated.

Figure 1. Electrocardiogram Traces of a Patient With Acquired QT Prolongation

(A) Marked QT prolongation and Torsades de pointes shown in 24-h electrocardiogram traces. (B) Prolonged QT interval was persistently observed after the initial episodes (corrected QT interval [QTc] 0.70 s ± 0.5). (C) Twelve-lead electrocardiogram 1 year before is normal (QTc 0.43 s ± 0.5).
In Western blotting of the lysate of HEK 293 cells expressing KCNH2, no band was detected in the presence of IgG from a healthy control subject (Fig. 2E, lane 1). A single distinct band of approximately 150 kDa was evident in the presence of IgG from the patient (Fig. 2E, lane 2). This band was absorbed by preincubation with the lysate of HEK 293 cells expressing KCNH2 protein (Fig. 2E, lane 3). A band of the same size was recognized in the presence of rabbit antiHERG polyclonal antibodies (Alomone Labs, Jerusalem, Israel) (Fig. 2E, lane 4).

A 155-kDa (upper) band is a mature form of the KCNH2 channel and a 135-kDa (lower) band is a precursor form of the KCNH2 channel (2). Figure 2B shows the upper band in the presence of the patient’s IgG. Therefore, the patient’s IgG contains autoantibodies against the mature form of KCNH2 protein.

Cross-reaction of anti-SSA/Ro antibodies with the L-type calcium channel has been reported (3). Lazzerini et al. (4) have also reported that patients with anti-SSA/Ro–positive connective tissue diseases show a high prevalence of QTc prolongation. In the present study, the patient had positive anti-SSA/Ro antibodies. Cross-reaction of anti-SSA/Ro antibodies with the KCNH2 channel may be involved in the pathogenesis of autoimmunity. Immunosuppressive therapy and reduction of plasma IgG may be effective for QT-interval shortening in the future. Further studies are needed to clarify this point.

In summary, our results show that abnormal IgG from a patient with acquired LQTS reduces the KCNH2 current and that the IgG includes anti-KCNH2 antibody. This is the first report of anti-KCNH2 antibody-induced LQTS.

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