Aborted Cardiac Arrest in a Patient Carrying KCNE1 D85N Variant during the Postpartum Period

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Abstract

The postpartum period is associated with an increased risk of fatal ventricular tachyarrhythmias in patients with congenital long QT syndrome (LQTS). We describe a 20-year-old female with LQTS who experienced aborted cardiac arrest during the postpartum period. Genetic screening identified a KCNE1 D85N variant, which has been reported to be a LQTS-causing gene variant, in the patient and her younger sister, whose QT interval was also prolonged. Since the allele frequency of this variant is almost 1%, it may be important to clarify whether such variant carriers indeed have an increased risk of fatal ventricular tachyarrhythmias during the postpartum period.

Key words: long QT syndrome, ventricular tachyarrhythmias, postpartum period, KCNE1

Introduction

The congenital long QT syndrome (LQTS) is an inherited disease characterized by prolongation of the QT interval in ECG, and is associated with fatal ventricular tachyarrhythmias resulting in sudden cardiac death. The postpartum period is associated with an increased risk of fatal ventricular tachyarrhythmias in the patients with LQTS (1), especially those with type 2 long QT syndrome (LQT2) (2, 3). KCNE1 D85N polymorphism has recently been reported to be a disease-causing gene variant in LQTS, and it may cause phenotypes similar to those observed in LQT2 (4). This report presents a female patient with LQTS, carrying a KCNE1 D85N variant, who experienced the first cardiac event during the postpartum period.

Case Report

The patient, a 20-year-old female, was referred to us in the context of an ECG abnormality at 17 years of age. Her 12-lead ECG presented with sinus bradycardia (heart rate: 46 bpm) and prolongation of the QT interval (QT/QTc interval: 554/515 ms) (Fig. 1A). She had never experienced cardiac events such as fainting and syncope. Echocardiography revealed no structural heart disease. An isoproterenol infusion test (1 μg/min) slightly prolonged the QTc interval from 515 ms to 550 ms (Fig. 1A). An investigation of her family members revealed that the QT interval of her younger sister was also prolonged (QT/QTc interval: 570/532 ms), and her heart rhythm was sinus bradycardia (heart rate: 47 bpm) (Fig. 1B), but she also remained asymptomatic. Their father had experienced an episode of syncope, but his ECG findings were not available. Therefore, the patient was diagnosed to have LQTS. The patient was subsequently followed annually without medication because she thereafter remained asymptomatic.

However, the patient abruptly lost consciousness during lactation at around 11 p.m. at 14 days after her first delivery when she was 20 years of age. About 10 minutes later when the emergency medical team arrived, she was unconscious, breathless, and had no pulse. Her heart rhythm showed ventricular fibrillation by an automated external defibrillator (AED). A discharge from the AED did not restore her normal heartbeat, but it instead caused cardiac arrest. She was finally resuscitated after her arrival at the hospital, and her

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heart began beating spontaneously, although her consciousness did not recover. Her blood test revealed no electrolyte disturbance. Chest X-ray revealed slight cardiomegaly (CTR: 54%) and slight congestion in the lung field (Fig. 1C), but blood oxygenation was not impaired. A 12-lead ECG just after resuscitation revealed sinus tachycardia (HR: 125 bpm) with prolongation of QT interval (QT/QTc interval: 400/588 ms) and ST changes in wide-ranging leads (Fig. 2). QT prolongation had been present throughout her hospitalization, especially QT prolongation (QT/QTc interval: 700/657 ms) with inverted T waves was prominent in a case of bradycardia (Fig. 2). Echocardiography showed that the left ventricular wall motion was moderately and diffusely impaired (ejection fraction: 36%). She died due to the complications of multiple organ failure two months after the cardiac event despite the administration of intensive care. An autopsy of the heart revealed no abnormality in the myocardium, such as myocardial disarrangement and infiltration of inflammatory cells, except for the necrosis of endomyocardium, possibly caused by the injury during cardiac arrest. This strongly suggests that her cardiac event had thus been caused by LQTS-related ventricular tachyarrhythmias.

We performed genetic screening of five major LQTS-causing genes, including KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 after obtaining the appropriate approval from the institution review board and written informed consent from these sisters. Nonsynonymous single nucleotide polymorphisms identified are listed in Table 1. The KCNE1 variant, D85N, which has been reported to be a disease-causing gene variant in LQTS (4), was identified in both the patient and her younger sister (Fig. 1D, Table 1). The KCNE1 S38G variant and the SCN5A H558R variant were also identified in both individuals (Table 1).

**Discussion**

The KCNE1 D85N had previously been thought to be a polymorphism because this allele frequency is as high as 0.7% in healthy Asians (5). However, Nishio et al recently reported that the D85N is indeed a disease-causing gene variant in LQTS (4). A functional analysis by Nishio et al. revealed that the D85N variant strongly suppresses KCNH2/
Figure 2. Time-dependent 12-lead ECG changes after resuscitation. Those recorded just after resuscitation, 8 hours later, 7 days later, 17 days later, and 25 days later are presented.

Table 1. The Results of the Genetic Screening for Five Major LQTS-causing Genes

<table>
<thead>
<tr>
<th>Genes</th>
<th>KCNQ1</th>
<th>KCNH2</th>
<th>KCNE1</th>
<th>KCNE2</th>
<th>SCN5A</th>
</tr>
</thead>
<tbody>
<tr>
<td>The patient</td>
<td>-</td>
<td>-</td>
<td>S38G (hm), D85N (ht)</td>
<td>-</td>
<td>H558R (hm)</td>
</tr>
<tr>
<td>A younger sister</td>
<td>-</td>
<td>-</td>
<td>S38G (ht), D85N (ht)</td>
<td>-</td>
<td>H558R (ht), L1988R (ht)</td>
</tr>
</tbody>
</table>

hm: homozygous, ht: heterozygous
Nonsynonymous single nucleotide polymorphisms are shown.

KCNE1 channels in comparison to KCNQ1/KCNE1 channels (4), which might explain the similarity of the phenotypes of the D85N carriers to those of LQT2 such as bradycardia. The D85N variant was thought to be the cause of LQTS in the patient, since no mutation in other LQTS-causing genes was identified, but the same gene variant, KCNE1 D85N, was also identified in her younger sister, furthermore, these sisters both showed sinus bradycardia.

In the D85N carriers, the mean QTc interval (498.5 versus 540.6 ms) is relatively shorter and the mean age at the occurrence of the first cardiac events (35.5 versus 21.0 years of age) is higher than those of other LQTS-causing gene mutation carriers, which is consistent with the functional analysis that exhibits mild reduction of channel function by the D85N variant (4). Furthermore, although the allele frequency of the D85N is high, all the D85N carriers do not always have prolonged QT interval or experience cardiac events. These findings led us to hypothesize that additional factor(s) may be involved in prolongation of the QT interval in the D85N carriers. Therefore, to improve the risk assessment, it is important to identify other factor(s) that modulate the QT interval in the D85N carriers. The patient and her sister have the KCNE1 S38G variant and the SCN5A H558R variant as well as the D85N variant. The KCNE1 S38G variant has not (6), suggesting that the SCN5A H558R variant may also have contributed to the prolongation of the QT interval in these sisters. A functional analysis of the SCN5A H558R variant did not exhibit gain of function of sodium currents which in turn prolongs cardiac repolarization (7). In contrast, the KCNE1 D85N variant suppressed the function of both KCNH2 and KCNQ1 (4). Therefore, from the viewpoint of genetic variants, the D85N variant was thought to be the main contributor to prolongation of the QT interval. The present case will provide a clue to the understanding of the increased risk of fatal ventricular tachyarrhythmias in patients carrying these genetic variants.

The risk of cardiac events in LQTS patients has been reported to increase during the postpartum period, especially in LQT2 patients (2, 3). The clinical features of the patient, such as bradycardia and the occurrence of the first cardiac event during the postpartum period, thus suggested that she had LQT2. However, the presence of any mutations in KCNH2 was excluded in both the patient and her younger sister. It seems quite reasonable to assume that the risk of cardiac events during the postpartum period in patients carrying the D85N variant is increased, because KCNH2-related channel function is also reduced in D85N carriers.

After the cardiac arrest, her 12-lead ECG presented with giant negative T waves in wide-ranging leads. These phenomena may be suggestive of other diseases such as myocarditis, Takotsubo cardiomyopathy and postpartum cardiomyopathy. However, since congestion in the chest X-ray was not strong, and blood oxygenation was not impaired after resuscitation, these diseases, if present, were not likely to be
related to the occurrence of the cardiac event. Otherwise, these ECG changes might have been caused by subendocardial ischemia due to a long-lasting cardiac arrest.

In conclusion, we present a case of LQTS carrying a disease-causing gene variant, KCNE1 D85N, who experienced the first cardiac event during the postpartum period. Since all D85N carriers do not always have prolonged QT interval or experience cardiac events, additional factor(s) such as the SCN5A H558R variant may also have been involved in the prolongation of the QT interval in this case. It is important to clarify whether D85N carriers indeed have an increased risk of fatal ventricular tachyarrhythmias during the postpartum period. If so, as the allele frequency of the D85N variant is almost as high as approximately 1% (4, 5), genetic testing before pregnancy should be performed in females with QT prolongation, even in those without symptoms, to avoid fatal ventricular tachyarrhythmias. Beta-blocker therapy for D85N carriers with particular attention paid to further bradycardia may reduce the risk of cardiac events during the postpartum period.

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References