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【 CASE REPORT 】

Symptomatic Long QT Syndrome Coexisting with Asymptomatic Acetylcholine-induced Vasospasm

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Abstract:

We herein report a rare case of long QT syndrome (LQTS) coexisting with acetylcholine (Ach)-induced vasospasm. A 31-year-old woman experienced cardiopulmonary arrest during running. LQTS was diagnosed by an electrocardiogram, and the coexistence of Ach-induced vasospam was determined by an Ach provocation test on coronary angiography. Although an implantable cardioverter defibrillator was placed, a beta-blocker was not prescribed for two reasons: first, the patient showed Ach-induced vasospasm alone with no symptoms and no ST change by Ach injection, and second, the use of beta-blockers alone in such patients carries a risk of vasospasm-induced ventricular fibrillation.

Key words: acetylcholine, long QT syndrome, vasospastic angina, ventricular fibrillation

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Introduction

Long QT syndrome (LQTS) is an inherited disease characterized by prolonged ventricular repolarization and the development of torsade de pointes (TdP) (1). Vasospastic angina (VSA) is a variant form of angina pectoris in which the symptoms mainly occur at rest (2). The occurrence of Tdp as well as vasospasm have been reported to be caused by an imbalance in autonomic nervous activity. Although beta-blocker is the first-line therapy for symptomatic LQT patients, beta-blocker alone is considered contraindicated for VSA patients, as it can induce vasospasm, resulting in sudden cardiac death (3). There have been few reports concerning the management of LQTS and VSA as coexisting diseases (4). However, although acetylcholine (Ach)-induced vasospasm as a subclinical form of VSA is sometimes observed when Ach provocation test is performed, its incidence and the potential risk of vasospasm remain unclear.

The present case report highlights the therapeutic strategy, including approaches to making decisions concerning beta-blocker use, for a patient with symptomatic LQTS and asymptomatic Ach-induced vasospasm.

Case Report

A 31-year-old woman was referred to our hospital because of a syncopal attack that occurred while running. She suffered from ventricular fibrillation (VF), as shown in Fig. 1a. A direct current shock was delivered, and return of spontaneous circulation was confirmed. Because the patient's conscious level was clear and her vital signs, including blood pressure, heart rate and oxygen saturation, were within the normal range, with no residual neurological sequela found, detailed examinations were performed after her arrival at our hospital. She had no remarkable family history and no chronic diseases that required oral medication.

A blood analysis showed no evidence of anemia, hypoglycemia or any inflammatory reactions. Furthermore, cardiac enzyme and electrolytes were within normal range. Although there was no ST segment change on an ECG, QT prolongation (QTc 471 ms) was found (Fig. 1b). A transthoracic echocardiogram showed a preserved ventricular function without severe valvular diseases. Coronary angiography was performed at the day of admission and revealed no organic stenosis. An Ach provocation test was then performed

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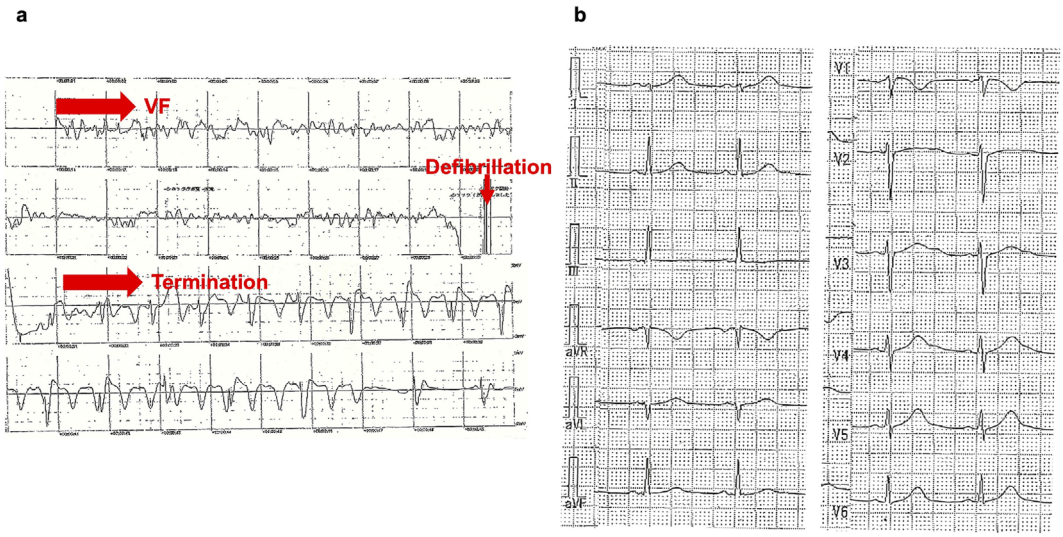

Figure 1. **a: An electrocardiogram (ECG) analyzed using an automatic external defibrillator. b: A 12-lead ECG performed at admission to our hospital. The corrected QT (QTc) interval was calculated using Bazett's formula. ECG showed a QTc prolongation of 471 ms.**

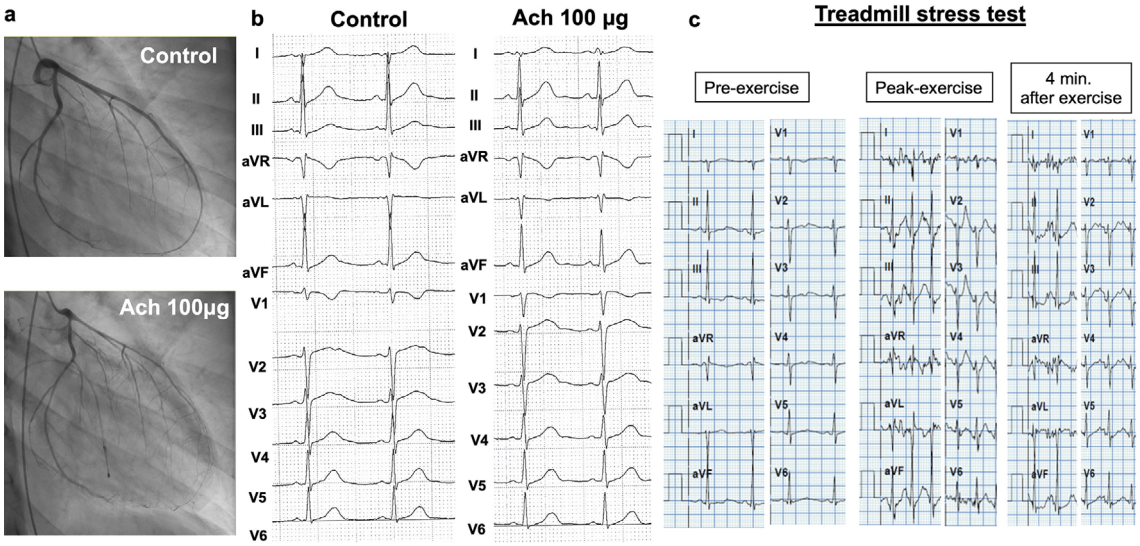

Figure 2. **a: Left coronary angiography (LCAG) with a right anterior oblique view. The upper panel shows LCAG at baseline as the control. The lower panel shows the diffuse vasospasm after acetylcholine 100 μg injection. Right CAG was not performed because severe spasm was detected in the left coronary artery. b: The ECG change after Ach injection into the LCA (right panel), compared with baseline (left panel). c: The treadmill stress test. QTc was calculated using Fridericia's formula.**

10 days after admission to confirm the presence or absence of VSA as a cause of cardiopulmonary arrest. Although Ach-induced coronary vasospasm was detected, there were no chest symptoms and no ST changes (Fig. 2a).

Interestingly, QTc interval prolongation from 458 ms to 469 ms was found after Ach 100 μg injection, as shown in Fig. 2b. Because LQTS was suspected as the underlying disease, a treadmill test was performed (Fig. 2c). The QTc interval was calculated using Fridericia' formula. The QTc interval was already prolonged (631 ms) at baseline, with a notched T in V2-5 leads, and remained prolonged at the peak of the stress test (QTc 566 ms), continuing for at least 4 minutes after the stress test had finished (QTc 495 ms). We therefore diagnosed the patient with LQTS based on her score of 6 points according to the Schwartz scoring system (QTc ≥480 ms, QTc >480 ms 4 minutes after stress, history of syncope and notched T wave). In addition, an epinephrine test was performed to classify the LQTS genotype (Fig. 3a), and the result suggested LQT2 (5). However, no mutation in KCNQ1, KCNH2 or SCN5A was found.

As secondary prevention, the patient underwent implantation of a subcutaneous implantable cardioverter defibrillator (S-ICD) (Fig. 3b). Beta-blocker was not prescribed because of the presence of the Ach-induced vasospasm. VF was not

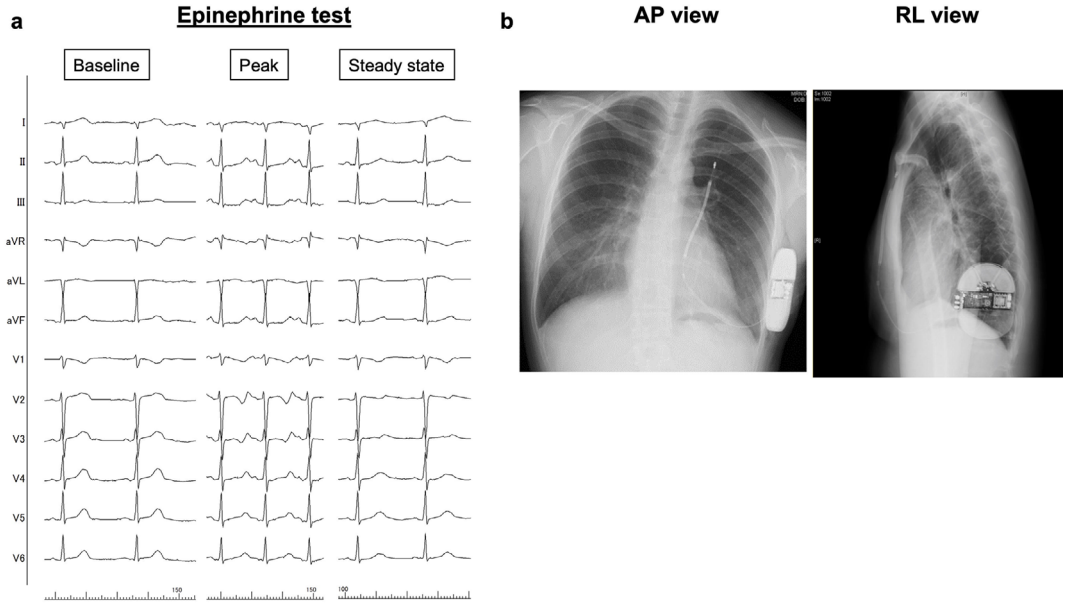

Figure 3. **a: The epinephrine test. The QTc interval was 417 ms at baseline, 579 ms at peak after 0.1 μg/kg epinephrine bolus injection, and 448 ms at steady state, 5 minutes after 0.1 μg/kg/min epinephrine drip infusion. b: Chest X-ray taken after the end of subcutaneous implantable cardioverter defibrillator (S-ICD) device implantation with an anterior to posterior view (AP) and right to left (RL) view.**

detected for 14 months after discharge, and there were no chest symptoms related to VSA. She continued to visit the outpatient clinic.

Discussion

The major findings of the present case are that symptomatic LQTS can coexist with Ach-induced coronary vasospasm, and therapeutic options should be considered based on which pathological condition is causing the symptoms.

At present, there are no data available concerning the prevalence of VSA with LQTS, including among the Japanese. Therefore, there have been few reports about the management of LQTS and VSA as coexisting diseases (6). With regard to the prevalence of Ach-induced vasospasm, Lee et al. analyzed 74 out of 1986 patients who survived out-of-hospital cardiac arrest and were angiographically diagnosed with coronary vasospasm. Among them, only one patient was diagnosed with LQTS (7). The coexistence of LQTS and Ach-induced vasospasm might therefore be extremely rare. Regarding the therapeutic strategy, although autonomic nervous imbalance can strongly affect the onset of symptoms in patients with LQTS as well as VSA, the indication for beta-blocker treatment differs completely between LQTS and VSA. Therefore, combination therapy with a calcium antagonist is recommended if the VSA patient needs a beta-blocker (2). For LQTS patients, a calcium antagonist was reported to be able to suppress the generation of premature ventricular contraction (PVC) due to early after depolarization and prevent the subsequent the PVC-induced TdP (8). In the present case, beta-blockers are expected to be effective, as VF occurred during exercise and her QT was prominently prolonged by epinephrine test. Although genetic testing revealed no LQT1-3-specific mutations, we should take into consideration the fact that gene mutations responsible for LQT are not detected in one-third of reported LQTS patients (9). Another possible gene mutation in the present case might be a ryanodine receptor (RyR2) mutation, which is a major mutation in catecholamine-sensitive polymorphic ventricular tachycardia (CPVT) that has recently been reported to overlap with LQTS (10).

Regarding the relationship between VSA and LQTS, QTc interval prolongation induced by Ach injection has been reported in patients with LQTS but not in patients without LQTS, and it increased marked spatial and temporal dispersion of ventricular repolarization, following short-long-short sequence of cardiac cycle. As a result, PVC falling on the preceding T wave triggered TdP (11). Although the risk of false positive may increase if an Ach provocation test is performed immediately after cardiopulmonary arrest, the difference in the response to Ach administration between the patients with and without LQTS can be useful for discriminating between the two groups and thereby reducing false positives. The combination of LQTS and VSA may therefore be more likely to cause ventricular arrhythmias and confer a high risk of sudden cardiac death.

Given that the incidence of VSA is high in East Asians including Japan, it is considered meaningful to perform the Ach provocation test in LQTS patients. This theory might be relevant to the current case, as the QTc interval was prolonged at the time of coronary vasospasm, so the use of vasodilators may have been considered. However, the pre-

sent patient showed only asymptomatic acetylcholine-induced vasospasm that did not meet the diagnostic criteria for vasospastic angina, and the risk of this for cardiopulmonary arrest was also difficult to evaluate. We decided to postpone the use of vasodilators for the time being. In addition, the administration of beta-blockers alone can increase the risk of inducing coronary spasm, so we decided not to prescribe any medication. If VF recurs in the future, a combination of calcium blockers and beta-blockers might be considered.

In conclusion, we should recognize that LQT can coexist with Ach-induced vasospasm, and the treatment strategy should be decided on a case-by-case basis.

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

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