Fragmented QRS is associated with torsades de pointes in patients with acquired long QT syndrome

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BACKGROUND Acquired long QT syndrome (LQTS) is a disease due to a secondary repolarization abnormality induced by various predisposing factors. In contrast to congenital LQTS, risk factors that produce acquired LQTS include organic heart diseases that often exhibit depolarization abnormality. Although various repolarization parameters have been evaluated in acquired LQTS, the existence of depolarization abnormality in association with torsades de pointes (TdP) has not been reported.

OBJECTIVE The purpose of this study was to evaluate both repolarization (QT components) and depolarization parameters (fragmented QRS [fQRS]) in acquired LQTS patients with markedly prolonged QT interval.

METHODS Seventy patients with acquired severe QT prolongation (QTc ≥550 ms) were studied. Thirty-two patients had syncope or TdP (syncope group). Thirty-eight patients did not have any symptoms (asymptomatic group). The existence of fQRS and QT components (QT, QTc, Tpe [interval between peak and end of T wave] intervals, and U-wave voltage) was analyzed.

RESULTS The syncope group had more frequent fQRS (81%) than did the asymptomatic group (21%, $P < .01$) and the incidence of fQRS was not different before and after removal of predisposing factors. The incidence of organic heart disease was not different between the two groups. No differences in QTc interval were noted between the syncope and asymptomatic groups, although the syncope group had longer QT and Tpe intervals and higher U wave than the asymptomatic group ($P < .01$).

CONCLUSION Acquired predisposing factors promoted repolarization abnormality (especially prolongation of QT and Tpe intervals), and the existence of fQRS had an important role in the development of TdP in patients with acquired LQTS.

KEYWORDS Acquired long QT syndrome; Fragmented QRS; Predisposing factor; Repolarization reserve; Torsades de pointes

ABBREVIATIONS **AP** = action potential; **ECG** = electrocardiogram; **fQRS** = fragmented QRS; **LQTS** = long QT syndrome; **NPV** = negative predictable value; **PPV** = positive predictable value; **QTp** = interval from onset of QRS to peak of T wave; **ROC** = receiver operating characteristic; **TdP** = torsades de pointes; **Tpe** = interval between peak and end of T wave

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Introduction

Secondary or acquired long QT syndrome (LQTS) occurs in association with various acquired factors, such as drugs that modulate cardiac ion channel function, hypopotassemia, and bradycardia.[1,2] Some patients with acquired LQTS experienced sudden syncope episodes due to polymorphic ventricular tachycardia torsades de pointes (TdP) that occasionally resulted in sudden cardiac death.[2] QT interval is one predictor of the occurrence of TdP in patients with acquired LQTS and in patients with congenital long QT syndrome,[3] whereas not all patients with prolonged QT interval experience TdP attacks.

Analysis of the QT interval (e.g., interval from onset of QRS to peak of T wave [QTp interval] and interval between peak and end of T wave [Tpe interval]) can represent transmural dispersion of repolarization and is a useful index of repolarization abnormality.[4–6] Manifest U wave also represents delayed repolarization.[7,8]

Although acquired LQTS is a disease due to acquired repolarization abnormality, depolarization abnormality also can have an important role in the development of TdP in acquired LQTS. The existence of organic heart disease[9,10] is also a risk factor for acquired LQTS. Myocardial injury and

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subsequent fibrosis progress in organic heart disease and become substrates for reentrant arrhythmias, but the role of conduction abnormality in the development of TdP in acquired LQTS has not been investigated.

Fragmented QRS (fQRS) is a convenient and useful marker that represents intraventricular zigzag propagation of the excitation.[11–13] It is evaluated by analyzing the 12-lead electrocardiogram (ECG). It is related to myocardial scaring and can be used to predict the prognosis of patients with various organic heart diseases.[11]

In the present study, we evaluated predisposing factors and ECG markers, including both depolarization abnormality (fQRS) and repolarization abnormality (various QT interval indices and U wave) in patients with acquired LQTS who had severely prolonged QT interval (corrected QTc according to Bazett formula, QTc ≥550 ms).

Methods

Patients

The study consisted of 70 patients (19 men and 51 women; mean age 68 ± 21 years) with acquired severe QT prolongation (QTc ≥550 ms) who were referred to Okayama University Hospital (n = 46) or Akaiwa Medical Association Hospital (n = 24). The patients were divided into two groups: (1) patients who had documented TdP or syncope episodes (TdP/syncope group; 28 patients with TdP and 4 patients with syncope) and (2) patients who had QT prolongation without syncope or TdP (asymptomatic group; 38 patients). The definition of acquired LQTS in this study was (1) detection of extreme QT prolongation (QTc ≥550 ms) with acquired predisposing factors, (2) no previous diagnosis of LQTS, and (3) no remarkable QT prolongation after removal of reversible predisposing factors (in narrow QRS patients: QTc ≤470 ms; in wide QRS [≥120 ms] patients, such as those with ventricular pacing or bundle branch block: QTc ≤500 ms).

ECG measurements

Standard 12-lead ECGs were recorded in all patients (filter range 0.15–100 Hz; AC filter 60 Hz, 25 mm/s, 10 mm/mV). ECGs were acquired at the time of maximum QT prolongation (asymptomatic group) or at the time of occurrence of TdP or syncope (syncope group). ECGs were also recorded as controls after reversible predisposing factors of acquired LQTS were removed.

RR, QRS, QT, QTc, QTp, and Tpe intervals and U-wave voltage were evaluated (Figure 1). QT intervals and T-wave morphology in lead V_5 and U wave in lead V_3 or V_4 were evaluated. T-wave morphology was classified according to the genotype–phenotype correlation of the congenital long QT syndrome as follows[14]: (1) broad-based T wave; (2) flat, notched T wave; and (3) late-appearance T wave. The existence of the complex T-wave abnormalities (negative T wave and T wave alternans) also was evaluated (Figure 1).

The existence of fQRS on 12-lead ECG was defined according to a previous study.[11–13] In patients with narrow QRS (QRS <120 ms), fQRS includes the presence of an additional R wave (R′) or notching in the nadir of the R wave or the S wave, or the presence of one R′ (fragmentation) in two contiguous leads. Incomplete right bundle branch block was excluded from the definition of fQRS. In patients with wide QRS (bundle branch block or ventricular pacing), fQRS was defined as two notches in the R or S wave in two contiguous leads.

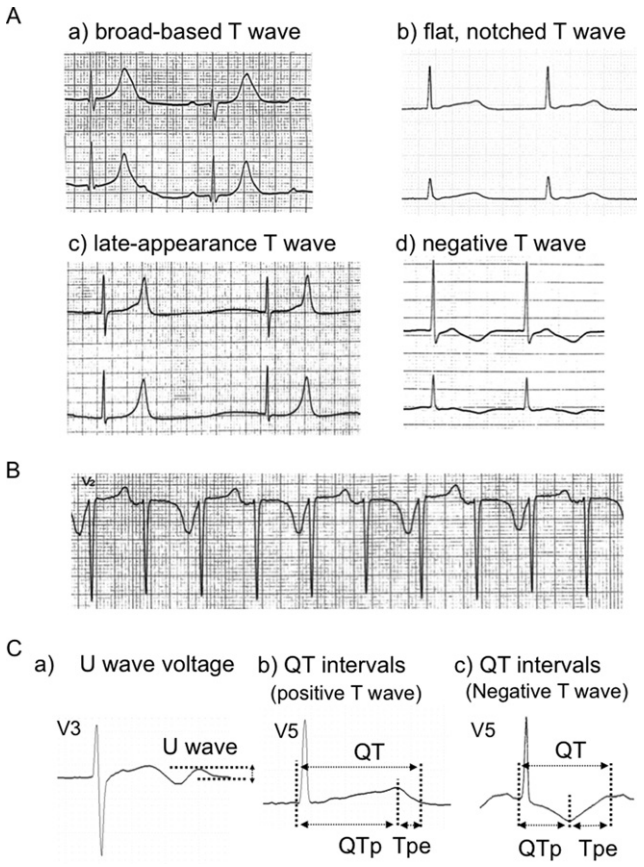

Figure 1 Classification of ECG morphology. **A:** T-wave morphology in leads V_5 and V_6. **(a)** Broad-based T wave, **(b)** flat and notched T wave, **(c)** late-appearance T wave, and **(d)** negative T wave. **B:** Occurrence of T-wave alternans. Lead V_2 shows that T-wave polarity changes beat by beat. **C:** Measurements of QT intervals and U-wave voltage. QTp = interval between onset and peak of T wave; Tpe = interval between peak and termination of T wave.

Predisposing factors

Predisposing factors of QT prolongation in each patient were evaluated and the number of factors counted. The predisposing factors were (1) female gender[15]; (2) elderly patients[16] (≥70 years old); (3) drugs that have been reported to cause QT prolongation[1]; (4) mineral abnormalities (hypokalemia,[17] hypocalcemia[18]); (5) organic heart disease (including heart failure and left ventricular hypertrophy[10]); (6) arrhythmias[19,20]; (7) severe visceral dysfunction (e.g., hepatic and renal insufficiency)[2]; and (8) QT prolongation at baseline.[21] Drugs, mineral abnormality, and arrhythmias are considered reversible factors.