LONG-TERM FOLLOW-UP STUDY OF THREE PATIENTS WITH
THE LONG QT SYNDROME

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We studied three women with the long QT syndrome. They were aged 42, 52
and 25 years and had experienced recurrent syncopal attacks. We followed case
1 for 17, case 2 for 18, and case 3 for over 6 y. The attacks tended to occur
during the premenstrual stage in case 1 and case 2; case 3 often experienced attacks
after exercise. The QT(U)c intervals on admission were 0.68, 0.62, and 0.50 in
case 1, 2, and 3, respectively. Torsade de pointes followed by ventricular fi-
brillation was documented in case 1 and case 2. Although each was treated with
a beta-blocker, none was fully compliant with the regimen. In case 1, estrogen
therapy administered to maintain the hormonal balance premenstrually effect-
tively prevented attacks. Despite the inconsistent use of beta-blockers, the
attacks in case 1 and case 2 tended to decrease with age. Case 2 experienced no
attacks after menopause. Cause 3 took medication consistently and remained
free of attacks for over 6 y. Although she discontinued beta-blocker therapy
because of pregnancy, she has experienced no attacks to date. These case stud-
ies suggest that hormonal status may be important in the development of syn-
copal attacks in female patients with the long QT syndrome.

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THE long QT syndrome (LQTS) is char-
acterized by an idiopathic prolongation
of the QT interval and recurrent epi-
sodes of ventricular fibrillation (VF) fol-
lowed by syncpe. The mortality is generally
high in untreated cases. However, beta-
blocker therapy or left stellectomy has re-
duced the mortality!

We followed 3 female patients with the
LQTS, 2 for over 30 years combined, after
the first episode of syncpe. These patients
were not fully compliant with beta-blocker
regimens. The third patient, who took prop-
ranolol consistently for about 6 years, had an
uneventful course. Although medication was
discontinued for pregnancy, she has experi-
enced no attacks to date.

CASE REPORT

Case 1: 42-year-old female
This patient experienced her first fainting
attack at the age of 14 years and epilepsy
was diagnosed. Despite anti-epileptie ther-
apy, she experienced recurrent episodes of
syncpe until the age of 25 when she tended
to experience the attacks before menstrua-
Case 1.

A) The QT(U)c interval was prolonged at 0.68 in lead V2.

B) Torsade de pointes followed by ventricular fibrillation.

Fig. 1. ECG on admission in case 1.

Physical examination showed normal findings. There was no deafness and laboratory findings were negative. Family history suggested the presence of Romano-Ward syndrome in the patient's mother and sister. The electrocardiogram (ECG) revealed a marked prolongation of the QT(U)c interval (0.68) (Fig. 1A). While in the hospital, the patient experienced several syncopal attacks accompanied by torsades de pointes (TDP) followed by VF (Fig. 1B). These attacks were provoked by loud voices, sounds, or extreme emotional stress. Although these attacks were usually controlled by the intravenous administration of lidocaine, DC shock was sometimes required.

Estrogen therapy prescribed in an attempt to maintain the balance with progesterone effectively prevented attacks. The patient refused hormonal therapy following discharge, but was successfully treated with pindolol (1–3 mg/day) at the outpatient clinic. She remained on this program for over 10 years, experiencing only one episode of syncope during that time (in October, 1979), despite her intermittent use of medication. Over the next 7 years, the patient took carteolol (5 mg/day) intermittently. She has experienced no serious attacks to date. Her clinical course and changes in the QT(U)c interval are shown in Fig. 2. The QT(U)c interval was variable, with no tendency for shortening seen with age.

Case 2: 52-year-old female

This patient experienced her first syncopal attack at the age of 20. Although attacks subsequently occurred at the ages of 23, 25, and 26, she received no treatment because
Case 1.

Intermittent use of medicine and often non-medication

Pindolol 3 mg/day

Pindolol 1-3 mg/day

Carveolol 5 mg/day

Frequent syncope

Syncope (5 min)

9/3 - 10/27
1st Admission

10/8/79

1973

75

80

’85

’90

8/2/77

QT(U)c=0.61

10/1/80

QT(U)c=0.64

2/7/85

QT(U)c=0.65

7/20/89

QT(U)c=0.62

Fig.2. Clinical course and change of QT(U)c interval in case 1.

she always recovered spontaneously. At the age of 34, she was admitted to hospital for evaluation of syncope. Over the next 11 years, she was admitted 8 times because of syncopal attacks. The attacks occurred during the 7 to 10 days preceding menstruation and were triggered by mental stress or loud sounds or voices. A feeling of chest discomfort preceded each attack. The family history was unremarkable.

The ECG on her first admission showed prolongation of the QT(U)c interval (0.62) with biphasic configuration of T(U) waves (Fig. 3A). TDP followed by VF was also seen (Fig. 3B). Multifocal ventricular extrasystoles and ventricular flutter were also observed. No abnormalities were observed on electrophysiological study, coronary angiography, or myocardial biopsy. A relationship between TDP and menstruation was strongly suggested, but hormonal therapy was not prescribed. Low-dose pindolol therapy (1–3 mg/day) was usually successful in preventing the episodes of syncope, except during the premenstrual period.

The frequency of attacks tended to decrease with age. This patient has now been followed for over 18 years, and no significant attacks have occurred over the past 10 years. Although she sometimes experienced minor symptoms because of arrhythmia, e.g., dizziness or chest discomfort, she has been symptom-free since menopause in July, 1989. The QT(U)c interval showed no tendency toward shortening with age. Her clinical course and the changes in the QT(U)c interval are shown in Fig. 4.

Case 3: 25-year-old female

At the age of 8, this patient developed palpitations followed by faintness during exercise. She experienced similar episodes once or twice a year until the age of 15. She remained free of attacks over the next 4 years. At 19 years of age, she experienced a fainting attack triggered by strong mental stress. At 20 years of age, she was admitted to hospital for evaluation of these symptoms. Her
Case 2.

A) 3/30/71

QT(U)c = 0.62

B) Torsade de Pointes

Fig.3. ECG on admission in case 2.
A) The QT(U)c interval was prolonged 0.62 in lead V2. U wave was prominent in precordial leads.
B) Torsade de pointes followed by ventricular fibrillation.

family history was negative. She began menstruating at the age of 11, but the relationship between menstrual periods and attacks was not clear.

The ECG showed a prolongation of the QT(U)c interval (0.50), sometimes in association with prominent U waves (Fig. 5). After exercise, the QT(U)c interval was paradoxically prolonged from 0.44 to 0.61 (Fig. 6). Electrophysiological study, coronary angiography, and myocardial biopsy showed essentially normal findings. The patient started propranolol therapy, 30—60 mg/day, and has experienced no further episodes to date. She became pregnant in December, 1990. Although medication was discontinued during pregnancy, she experienced no serious attacks. The latest QT(U)c interval, measured after discontinuation of propranolol, was 0.56.

DISCUSSION

The mortality associated with the Romano-Ward syndrome is generally high in untreated cases. Schwartz et al! reported a 71% mortality in symptomatic untreated patients. Daily administration of a beta-blocker or high left thoracic sympathectomy reduces the mortality by about 6%. The 15-year mortality for patients treated with beta-blocker is 9%; for untreated patients, or those treated with other modalities, the mortality is 53%, underscoring the ability of beta-blocker therapy and left stelllectomy to prevent ventricular arrhythmias.

Despite their inconsistent use of beta-blockers, often going for months without treatment, cases 1 and 2 have done well for prolonged periods (17 years and 18 years, respectively). Case 1 has survived for over
Case 2.

Intermittent use of medicine and often non-medication

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† Propranolol 20-30 mg/day

1 2 3 4 5 6 7

Fig. 4. Clinical course and change of QT(U)c interval in case 2. The T(U) wave showed variations, but the QT(U)c interval showed no tendency toward shortening.

28 years since the initial syncope, and case 2 has survived for 32 years. Both patients had experienced frequent premenstrual episodes of syncope with a marked prolongation of the QT(U) interval followed by VF. Although syncopal episodes have been found to be associated with menses in 9% of cases, we were unable to find a detailed description of hormonal therapy for LQTS. Estrogen therapy was effective in case 1 during hospitalization, however, any long-term efficacy is unclear because the patient refused to continue therapy. Syncopal attacks were also associated with the premenstrual period in case 2. In addition, case 2 became completely symptomfree after menopause, and the case 3 patient experienced no symptoms after pregnancy despite a lack of medication. These observations suggest hormonal balance plays an important role in the development of syncopal episodes in female patients.

It is also possible that increasing age may have contributed significantly to the decreased frequency of syncope. Hashiba et al reported that the QT interval in male patients with the Romano-Ward syndrome became shorter with age. Our patients did not show a shortening of the QT(U)c interval, suggesting that hormonal status, rather than age, may be a more important factor of the LQTS syndrome in women.

Case 3 showed paradoxical prolongation of the QT(U)c interval after exercise, which sometimes happens in the LQTS! Weintraub et al have suggested that factors other than a delay in adaptation to heart rate may influence the QT interval in the LQTS. TDP followed by VF was suspected as the mechanism of syncope in this patient during the attacks because other possible causes of syncope were ruled out. The patient was successfully treated with daily low-dose propranolol therapy. This patient became

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Case 3.

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QT(U)c = 0.50 0.51 0.52

Fig. 5. ECG on admission in case 3. Prominent U wave was seen in lead V2.

pregnant and experienced no serious attacks for 7 years after her first admission.

Bruner et al4 also described a patient with idiopathic LQTS who was successfully treated with both low-dose beta-blocker therapy and left thoracic stelllectomy. When this patient became pregnant, her medication was discontinued at 5 weeks' gestation. She then remained free of attacks throughout pregnancy, labor, and postpartum follow-up. Bruner et al4 cautioned that the use of propranolol during pregnancy should be limited to life-threatening conditions because of the potential for effects such as intrauterine growth retardation and neonatal hypoglycemia. We discontinued propranolol.
administration in case 3 after she became pregnant. She remains free of syncopal episodes to date. However, Csanady et al\textsuperscript{5} described a patient with the Romano-Ward syndrome who had Adams-Stokes attacks caused by VF on the first postpartum day and during the premenstrual period. Her ECG showed prolongation of the QT interval and multifocal ventricular extrasystoles followed by VF. The QT interval and the grade of ventricular arrhythmias should be monitored throughout pregnancy with periodic ECG and Holter monitoring, as feasible.

Because our patients took their medications only inconsistently, their favorable clinical course may represent the natural evolution of their disease with age rather than a treatment effect. The premenstrual attacks might also have been simply a consequence of the irritability of these patient during these periods, as reported by Csanady et al\textsuperscript{5} However, hormonal status clearly emerged as an important factor in the development of syncopal attacks in these female patients with the LQTS. The efficacy of beta-blockers in preventing the attacks is established. Control of hormonal imbalance may provide an effective additional therapeutic strategy.

REFERENCES