Idiopathic Long QT Syndrome With Early Afterdepolarization Induced by Epinephrine

— A Case Report —

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A patient with idiopathic long QT syndrome had repeated syncopal episodes. The QTc interval on the electrocardiogram at rest was 530ms and was prolonged by exercise up to 740ms with T wave alternation. Intravenous epinephrine (0.1 µg/kg weight per min), but not isoproterenol (0.7 µg/min), produced early afterdepolarization of the monophasic action potential recorded at the right ventricular apex. Epinephrine prolonged the QTc interval to 710ms. After the addition of propranolol to the epinephrine, the QTc (580ms) was longer than at baseline. Methoxamine also prolonged the QTc to 580ms. The QT interval in long QT syndrome is generally considered to be prolonged by a β -adrenergic effect, but in the present case β -adrenergic stimulation had an additional effect on the prolongation of the QT interval. (Circ J 2004; 68: 587–591)

Key Words: β -Adrenergic receptor; Early afterdepolarization; Epinephrine; ^{123}I -metaiodobenzylguanidine (MIBG) scintigraphy; Idiopathic long QT syndrome; Monophasic action potential

Torsade de pointes is the major tachyarrhythmia found in patients with long QT syndrome (LQTS) and several investigators report that the underlying mechanism is closely related to early afterdepolarization (EAD).^{1,2} Epinephrine and isoproterenol both induce fatal arrhythmias³ in patients with LQTS; in an electrophysiological study with catecholamine infusion, the monophasic action potential (MAP) recording often revealed an abnormal repolarization called a ‘hump’, which is direct evidence of EAD.^{1,3–5} The prolongation of the QT interval and the occurrence of hump in LQTS are generally considered to be promoted by β -adrenergic effects; however, the role of β -adrenergic effects on the QT interval has been relatively neglected.^{6,7}

In a recent case, we observed that the MAP recording showed the hump with epinephrine infusion, but not with isoproterenol infusion. The addition of β -adrenergic stimulation to the β -adrenergic stimulation had a greater effect on the prolongation of the QT interval and hump than β -adrenergic stimulation alone. This finding suggests that in some patients with LQTS, β -adrenergic stimulation has an additional role in exacerbating the arrhythmia resulting from increasing EAD amplitude and prolongation of the QT interval under β -adrenergic stimulation.

Case Report

A 50-year-old woman was admitted to hospital because

of a syncopal attack that occurred suddenly while she was talking to her daughter. She recovered consciousness in a few minutes; however, she was stuporous and responded very slowly on arrival in the emergency ward, but readily recovered.

She had a history of occasionally feeling faint for a few minutes accompanied by palpitations, which had been diagnosed as epilepsy when she was 8 years old. There was a family history of syncopal attacks in her brother and her nephew. Her mother was suddenly died at 53 years old from an unknown cause (Fig 1).

Physical examination revealed no abnormalities other than mild hypertension (166/92 mmHg). The electrocardiogram on admission revealed a marked prolongation of the QT interval up to 540 ms (QTc=530 ms) (Fig 2). Serum electrolyte concentrations were within normal limits (Na 137 mmol/L, K 3.5 mmol/L, Cl 104 mmol/L, Ca 8.2 mg/dl, Mg 2.0 mg/dl). The chest X-ray showed cardiomegaly (car-

Fig 1. Family pedigree of the patient (arrow). Men are denoted by squares and women by circles. Solid symbols denote long QT syndrome (LQTS) and hatched symbols denote a history of syncope. The patient's mother died suddenly from an unknown cause.

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Fig2. ECG on admission shows normal sinus rhythm with marked prolongation of the QT interval (QT/QTc: 540ms/530ms) (Left). Both QT and QTc were prolonged during recovery, accompanied by high blood pressure. Maximal QTc was 740ms (Right).

Fig 3. ECG on admission with T wave alternation at 3 min after the endpoint.

Fig 4. Changes in the ECG with infusion of sympathomimetic drugs: isoproterenol ($0.7 \mu\text{g}/\text{min}$), epinephrine ($0.1 \mu\text{g}/\text{kg}$ body weight per min), norepinephrine ($0.5 \mu\text{g}/\text{kg}$ body weight per min) and methoxamine ($12 \mu\text{g}/\text{kg}$ body weight per min). All of the drugs prolonged the QTc interval, and epinephrine had the maximum effect. After the addition of propranolol ($0.67 \text{ mg}/\text{kg}$) to the epinephrine, the prolongation of QT interval was suppressed, but was not completely restored to the baseline.

Fig 5. Intracardiac ECG and MAP recorded at the right ventricular apex under continuous atrial pacing (120 beats/min) in the control, with the infusion of isoproterenol, and with the infusion of epinephrine. QT interval and MAPD₉₀ was markedly prolonged by epinephrine. The hump pattern of the MAP occurred reproducibly only with the infusion of epinephrine.

diothoracic ratio=55%), but there was not any pulmonary venous congestion. Echocardiography was normal.

During exercise on an ergometer, the QT and QTc interval gradually shortened as the heart rate increased. Maximal prolongation of QT and QTc were observed at the end of exercising, accompanied by higher blood pressure: the maximal QTc was 740 ms with T wave alternation at 3 min after the endpoint, when she complained of leg fatigue at 70 W loading (Figs 2,3).

We tested the effects of intravenous administration of autonomic drugs: isoproterenol (0.7 µg/min), epinephrine (0.1 µg/kg body weight per min), norepinephrine (0.5 µg/kg body weight per min) and methoxamine (12 µg/kg body weight per min) (Fig 4). The dosages were determined by our standard that her systolic blood pressure reached 200 mmHg or heart rate 120 beats/min. All of the drugs prolonged QTc and the effect of epinephrine was the greatest. After the addition of propranolol (0.67 mg/kg) to the epinephrine, the QTc interval was almost restored to the baseline. Her heart rate did not increase during the infusion of norepinephrine, methoxamine or after propranolol was added to epinephrine, but isoproterenol and epinephrine increased both heart rate and systolic blood pressure.

In previous reports, a hump pattern of the MAP has been shown to indicate EAD.^{1,4,5} In order to evaluate the effects of the drugs on EAD, we recorded the MAP under constant atrial pacing at a cycle length of 500 ms during infusion of isoproterenol (1.0 µg/min) or epinephrine (0.1 µg/kg body weight per min) (Fig 4).⁸ The QT interval and duration of the MAP at 90% repolarization (MAPD₉₀) were measured at the end of a sequence of paced beats to avoid interruption by the next pacing spike.

In the control state, the QTc interval was 570 ms, MAPD₉₀ was 330 ms and the hump pattern did not occur. Isoproterenol prolonged the QTc to 620 ms, but not the QT interval or MAPD₉₀. During the infusion of epinephrine, the QTc was prolonged to 760 ms and MAPD₉₀ to 460 ms, and the hump pattern occurred reproducibly only in the presence of epinephrine (Fig 4). Programmed ventricular stimulation (RV burst, RV single and double extrastimuli) with infusion of isoproterenol or epinephrine did not induce ventricular tachyarrhythmias.

We assessed sympathetic nerve activity by ¹²³I-metaiodobenzylguanidine (MIBG) scintigraphy. The planar view images were obtained at 20 min and 4 h after injection of radioisotope without any other drugs. There was no cardiac uptake of ¹²³I-MIBG on images from either time period.

We treated her with β -adrenergic antagonists and she has been free of her symptoms, such as palpitations or syncope, for 1 year.

Discussion

Sympathetic stimulation, exercise tests and administration of exogenous catecholamines are known to induce QT prolongation and torsade de pointes, which are associated with syncope or sudden cardiac death, in patients with congenital LQTS. The occurrence of cardiac arrhythmias and sudden death in LQT1 patients is often associated with adrenergic stimulation such as physical or emotional stress. A net increase in the outward repolarizing current (I_{Ks} and I_{Cl} vs I_{Ca}) usually occurs in response to adrenergic stimulation and is considered to underlie the abbreviation of the action potential duration (APD) and QT interval under normal conditions. A smaller increase in I_{Ks} could upset

this balance and account for the failure of adrenergic stimulation to abbreviate APD and QT interval in LQT1 patients.^{9,10}

The protection against sudden death associated with the use of β -blockers¹¹ and with stellate ganglionectomy¹² confirms the importance of sympathetic stimulation as a trigger of arrhythmias. The difference in the effectiveness of β -blockers and stellate ganglionectomy implies a role of the β -adrenoreceptor in the process. Reports of the inhibitory effect of β -blockade on the QT prolongation caused by exercise also suggest an additional role of β -adrenoreceptor.^{7,9,13}

The different effect of several catecholamines in patients with LQTS has not been reported. The present case suggests that there are several reasons why stimulation of the β -adrenoreceptor had an additional effect on QT prolongation. First, epinephrine caused the maximal prolongation of QTc among the various catecholamines tested in our study. After the addition of propranolol to epinephrine, the prolongation of the QT interval was suppressed, but it was not completely restored to the baseline. Methoxamine also prolonged the QT interval. Second, isoproterenol did not induce the hump pattern of the MAP during an electrophysiological study, but epinephrine did. These findings suggest that β -adrenergic stimulation alone can prolong the QT interval and thus have arrhythmogenic effects such as induction of EAD or prolonging the QT interval.

Some researchers have reported a vagal influence on QT prolongation in LQTS.^{14,15} After termination of exercise, sympathetic tone decreases immediately, but vagal tone decreases slowly and the different time course of autonomic recovery could explain the phenomenon we observed (see Fig 2). Furthermore, β -adrenergic stimulation activates the vagal nerve as a reflex, which may be clinically important, when the β -adrenoreceptor has prolonged the QT interval.

¹²³I-MIBG scintigraphy is used as a non-invasive means of detecting impaired presynaptic cardiac sympathetic nerve endings. In the present case, it showed the complete absence of cardiac accumulation of the isotope in both the early and late image. This observation is unusual because only segmented decrease caused by irregular regional sympathetic innervation has been reported.^{11,12} A defect on the early image has been recorded under the following conditions: sympathetic denervation,¹³ heart failure,¹⁴ orthostatic hypotension,¹⁵ diabetes mellitus¹⁶ and cardiomyopathy. The patient presented here did not have any of these conditions. The total lack of accumulation of MIBG implies a broad cardiac sympathetic impairment.

We prescribed a β -blocker (propranolol 30 mg/day) and followed up the patient for 1 year, which is conventional therapy. She has been free of any symptoms such as palpitations or syncope. If her symptoms ever relapse, we will prescribe additional β -adrenergic antagonists.

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