Journal of Cardiology 23: 99–106, 1993

Torsades de pointes associated with acquired long QT syndrome: Observation of 7 cases

Naohiko TAKAHASHI
Morio ITO
Toshio INOUE
Kousei KOUMATSU
Yasushi TAKESHITA*
Shigeru TSUMABUKI*
Masamichi TAMURA*
Ken INOUE*
Toshihiro MAEDA*
Tetsunori SAIKAWA*

Summary

We examined the clinical characteristics and electrocardiographic findings of 7 patients having the acquired long QT syndrome who developed torsades de pointes while receiving no antiarrhythmic drugs. A total of 43 episodes of torsades de pointes were documented among these patients. Underlying heart diseases were present in 6 patients and hypopotassemia (≦3.3 mEq/*l*) in 4. Four had bradycardia (≦52 beats/min) immediately before the development of torsades de pointes. The QTc intervals measured immediately before the episodes of torsades de pointes were significantly longer than those 6–24 hours before the episodes (0.69±0.10 vs 0.56±0.10 sec, $p<0.05$), while heart rates did not differ significantly between these 2 periods (54±12 vs 58±15 beats/min). The ventricular rate of torsades de pointes was 192±24 beats/min. A "long-short initiating cycle" was noted in all 43 episodes, and the initiating premature ventricular beat (PVB) showed the "R on T(U)" phenomenon in 42 of the episodes. A notched T-U complex due to a prominent slow wave (U wave) at the end of the T wave was noted in 5 patients immediately before the episodes of torsades de pointes. Prolongation of the preceding RR interval was directly related to the increase of the U wave amplitude, which caused an increased likelihood of the occurrence of PVBs near the peak of the U wave. Torsades de pointes developed from the largest U wave.

Direct current cardioversion was transiently effective for treating torsades de pointes, and intravenous lidocaine, atropine and verapamil were effective in some cases. In 4 patients with hypopotassemia, potassium supplement completely abolished torsades de pointes.

大分医科大学　臨床検査医学
*同　内科第一
大分県大分郡挾間町医大ヶ丘 1-1 (〒879-55)

The Department of Laboratory Medicine and *the First Department of Internal Medicine, Oita Medical University, Idaigaoka 1-1, Hazama-cho, Oita-gun, Oita 879-55

Received for publication August 5, 1991; accepted March 30, 1992 (Ref. No. 38–142)

These results indicated that 1) hypopotassemia and bradycardia were important precipitating factors for the development of torsades de pointes, and 2) increased U wave amplitude due to the prolongation of the preceding RR interval was directly related to the development of torsades de pointes.

Key words
Acquired long QT syndrome Hypopotassemia Bradycardia U wave Early afterdepolarization

Introduction

"Torsades de pointes" (TdP) is a distinct form of ventricular tachyarrhythmia characterized by a QT prolongation and paroxysms of ventricular tachycardia with polymorphic QRS complexes revolving around an isoelectric line[1]. Torsades de pointes occurs when QT interval prolongation predominates, either as an inherited or acquired abnormality[1-3]. Most common of the acquired long QT syndromes is that associated with the administration of antiarrhythmic drugs[1-5]. This syndrome is also caused by electrolyte abnormalities (hypopotassemia, hypocalcemia and hypomagnesemia), or severe bradyarrhythmias[1-5].

Seven cases of the acquired long QT syndrome who developed torsades de pointes while receiving no antiarrhythmic drugs are reported here. The purpose of the present study was to examine the clinical characteristics and electrocardiographic warning signs which precede the development of torsades de pointes. The results showed that most patients had hypopotassemia, bradycardia or both, and that the development of torsades de pointes was closely related to the enhanced U wave which was caused by prolongation of the preceding RR interval.

Subjects and methods

Seven patients (2 men and 5 women) with the acquired long QT syndrome who developed torsades de pointes while receiving no antiarrhythmic drugs were observed (**Table 1**). Their ages ranged from 44–90 years (mean ± SD: 73 ± 16 years). Torsades de pointes consisted of 6 or more successive premature ventricular beats (PVBs) with polymorphic QRS complexes revolving around an isoelectric line[1]. We analyzed 43 episodes of torsades de pointes documented in these patients. The parameters measured in the standard 12-lead electrocardiograms included: 1) the RR interval, 2) the QT and QTc intervals, 3) the amplitudes of the U waves relative to the T wave amplitudes (U/T ratio), 4) the coupling intervals of the initiating PVB of the torsades de pointes, and 5) the ventricular rate of torsades de pointes. The QT interval was measured in the lateral precordial leads and the QTc interval was calculated using Bazett's formula (QT interval in seconds divided by the square root of the preceding RR interval in seconds)[7]. In the present study, a prominent slow wave was frequently observed in the descending limbs of the T wave (see **Figs. 2 & 3,** arrows). We regarded this "slow wave" as the "U wave". The U wave was included in the measurement of the QT interval. Measurements were made from the electrocardiographic tracings recorded immediately (pre-TdP) and 6–24 hours before the development of torsades de pointes (baseline). The rate of torsades de pointes was calculated by averaging the cycle lengths for the initial 6 beats of torsades de pointes.

Data were reported as mean ± SD unless otherwise specified. Statistical comparisons of the data were made by the Student's t-test. A p value of less than 0.05 was considered significant.

Results

Table 1 shows the clinical characteristics of 7 of the patients studied. Six patients had underlying heart disease; 4 of them had congestive heart failure. Four patients had serum potassium concentrations of 3.3 mEq/*l* or less (normal range: 3.5–5.3 mEq/*l*). Three of these

Table 1. Clinical characteristics of 7 cases

Case No.	Age/sex	Underlying heart disease	Basic rhythm	Drug	Electrolytes		Treatment
					K (mEq/*l*)	Ca (mg/d*l*)	
1	44/F	CHF (uterine ca)	Sinus	Furosemide	3.0	7.4	DC cardioversion*, lidocaine#, verapamil, K correction
2	80/M	None	Sinus	None	2.1	11.6	DC cardioversion*, K correction
3	83/M	CHF (MR)	Complete A-V block	Furosemide, spironolactone, trichloromethiazide	4.1	9.1	NA
4	56/F	CHF (AR, MR)	Atrial fibrillation	Furosemide, spironolactone, digitoxin	3.3	8.2	DC cardioversion*, K correction
5	90/F	CHF (bile duct ca)	Complete A-V block	Furosemide	2.7	NA	Atropine, K correction
6	79/F	HHD	Sinus	None	4.1	8.1	Lidocaine, mexiletine
7	76/F	MR	Complete A-V block	Mefruside	3.7	8.2	DC cardioversion*, ventricular pacing

CHF=congestive heart failure; ca=cancer; MR=mitral regurgitation; AR=aortic regurgitation; HHD=hypertensive heart disease; DC=direct current; NA=not available; *=transiently effective; #=not effective.

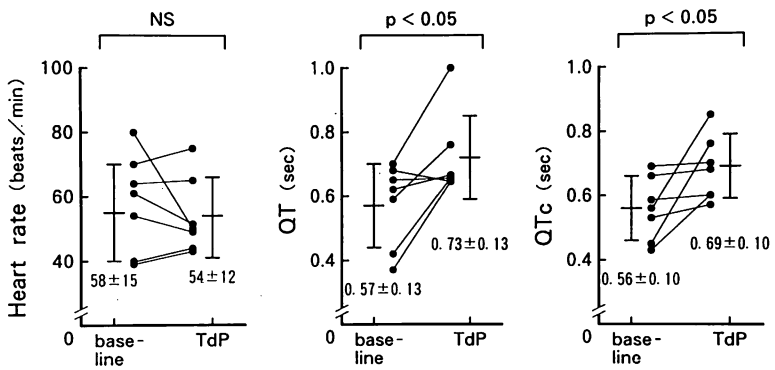

Fig. 1. Comparison of the heart rates and the QT and QTc intervals, recorded 6–24 hours (baseline) **and immediately** (pre-TdP) **before the development of torsades de pointes.**

4 patients received diuretics. Serum calcium concentrations were measured in 6 patients, and were within normal range (8.2–10.2 mg/d*l*) in 5. The basic cardiac rhythm was sinus rhythm in 3, junctional or idioventricular rhythm due to complete A-V block in 3, and atrial fibrillation in one. Five patients had a bradycardia (52 beats/min or less) at the pre-TdP period.

Fig. 1 compares the heart rates, QT and QTc intervals of 7 patients during the baseline and pre-TdP periods. Heart rates did not differ significantly between the 2 periods (54±12 vs 58± 15 beats/min). The QT and QTc intervals were significantly longer in the pre-TdP period than in the baseline period (0.73±0.13 vs 0.57± 0.13 sec, $p<0.05$; and 0.69±0.10 vs 0.56±

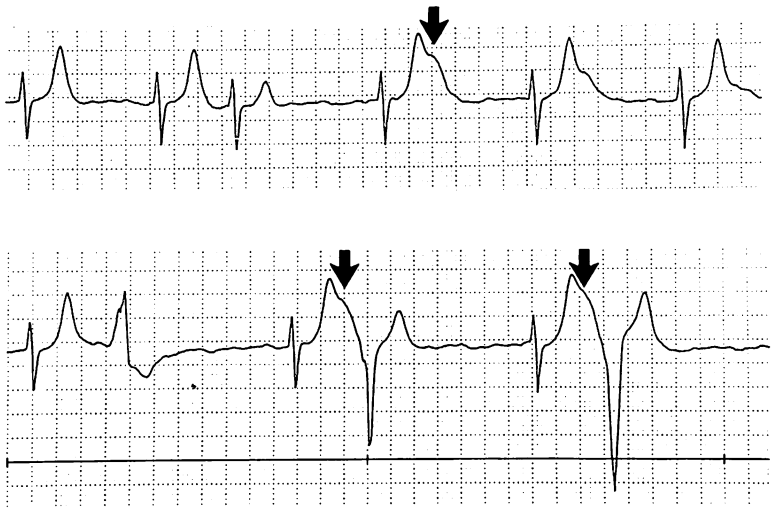

Fig. 2. Changes of T-U complex in association with the changes of the preceding RR interval observed in Case 4.

A prominent slow wave (U wave) at the end of the T wave was noted after a long RR interval (arrow in the upper trace). Premature ventricular beats occurred near the peak of the U waves (arrows in the lower trace).

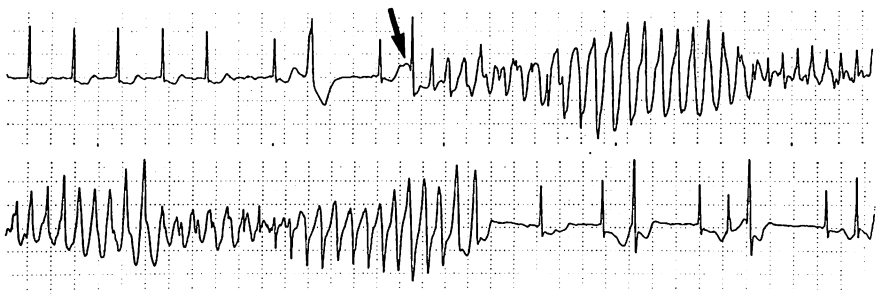

Fig. 3. One episode of torsades de pointes observed in Case 4.

The prolonged RR interval after a premature ventricular beat was followed by a marked increase of the U wave amplitude (arrow). The premature ventricular beat occurring near the peak of this large U wave triggered an episode of torsades de pointes.

0.10 sec, $p<0.05$). Seven patients had a total of 43 episodes of torsades de pointes. The mean rate of torsades de pointes was 192 ± 24 beats/min. A "long-short initiating cycle"[5,6] was noted in all the episodes. The mean coupling interval of the initiating PVB of torsades de pointes was 0.56 ± 0.10 sec. In 42 of the total 43 episodes of torsades de pointes, the PVB initiating the episodes of torsades de pointes showed the R on T (U) phenomenon.

In the pre-TdP period, 5 patients showed emergence of a prominent U wave at the end of the T wave (**Figs. 2 & 3,** arrows). In these patients, prolongation of the preceding RR interval caused a marked increase in the amplitude of the subsequent U wave, which was associated with the development of PVBs and torsades de pointes (**Figs. 2 & 3**). **Fig. 4** shows the relation-

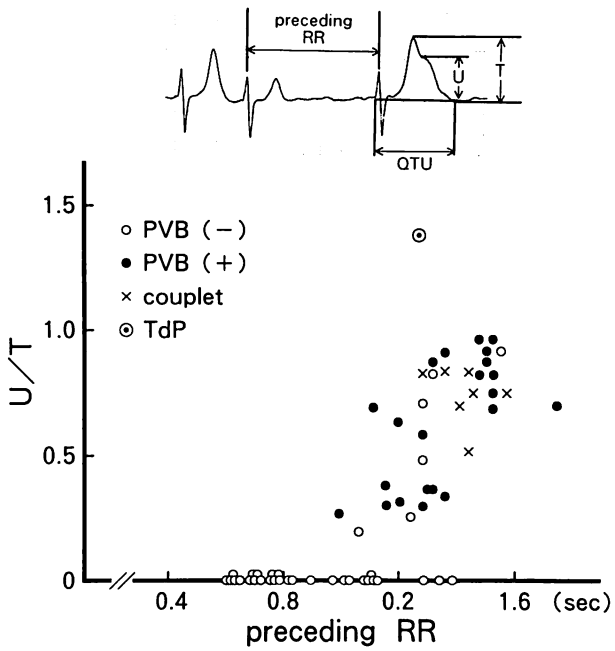

Fig. 4. The relationship between the preceding RR intervals and the U/T ratio observed in Case 4.

Data were obtained by measuring the consecutive 60 beats before one episode of torsades de pointes. The methods of measurements are shown above the figure.

Symbols ○, ●, ×, and ⊙ indicate the occurrence of no premature ventricular beat (PVB), single PVB, a couplet of PVBs and torsades de pointes from the T-U complex, respectively.

ship between the preceding RR interval and the U/T ratio obtained from one patient (Case 4). Data in this figure were obtained by measuring 60 consecutive beats just before one episode of torsades de pointes. The preceding RR interval was directly related to the increased U/T ratio and the occurrence of PVBs. Furthermore, this figure clearly demonstrates that the increase in the U wave amplitude was related to the increased likelihood of successive PVBs. Torsades de pointes developed in association with the greatest U/T ratios.

In our 7 patients, several therapeutic interventions were used to terminate and prevent torsades de pointes (**Table 1**). Most patients received more than one treatment. Direct current cardioversion performed for 4 patients was only transiently effective. Lidocaine infusion was administered to 2 patients, and effective in one in whom oral mexiletine prevented the development of torsades de pointes. In another patient who did not respond to lidocaine, intravenous verapamil (5 mg) was effective in suppressing torsades de pointes. Intravenous atropine (0.5 mg) was effective in one patient. In one patient with complete A-V block, temporal ventricular pacing was very effective, and a permanent pacemaker was implanted. In 4 patients with hypopotassemia, correction of their serum potassium concentrations resulted in complete resolution of torsades de pointes.

Discussion

Seven patients with the acquired long QT syndrome who developed torsades de pointes while receiving no antiarrhythmic drugs were studied. The most common cause of the acquired long QT syndrome is reportedly the ad-

ministration of antiarrhythmic drugs such as quinidine[1-5]. Other factors have also been implicated in the induction of this syndrome, including hypopotassemia, severe bradycardia, and malnutrition (liquid protein modified fast diet and starvation)[1-3]. Most of our patients had hypopotassemia, bradycardia or both.

In the present study, a " long-short initiating cycle "[5,6] was observed in all of the 43 episodes of torsades de pointes, and most episodes (42 of 43) were triggered by PVB showing the " R on T (U) " phenomenon. Prolongation of the preceding RR interval was directly related to QT prolongation and the increased U wave amplitude. In addition, increase in the U wave amplitude was directly related to the development of PVBs and torsades de pointes near the peak of the U wave (**Figs. 2 & 3**). These results were consistent with those previously reported[1-4]. To our knowledge, this is the first report of an evaluation of the quantitative relationships among the preceding RR interval, the U wave amplitude and the occurrence of ventricular arrhythmias (**Fig. 4**). The present study showed that episodes of torsades de pointes arose from a prominent slow wave at the end of the T wave. We designated this " slow wave " the " U wave ".

As for mechanisms for the genesis of such a slow wave, several possibilities have been considered[2]: 1) an abnormal increase in the normal U wave amplitude, 2) an abnormal distortion of the T wave, i.e., a reflection of heterogeneity of ventricular repolarization, and 3) a " diastolic wave " distinct from normal T and U waves. Although the electrophysiological mechanisms of the slow waves (U waves) in patients with long QT syndrome remain unknown, recent clinical and animal studies[8-10] suggested that torsades de pointes might be triggered by activity occurring early afterdepolarizations (EADs) and that the slow waves might be related to EADs in the ventricular muscles. El-Sherif et al[8] demonstrated the occurrence of EADs in a patient with quinidine-induced torsades de pointes by recording the monophasic action potential from the right ventricle. They also reported that EADs were manifest when the preceding RR interval was prolonged, and the timing of EADs was identical to that of the slow waves in surface electrocardiograms. The same findings were observed in their experimental canine model of the long QT syndrome[9]. We also reported in vivo evidence of EADs and triggered activity as the underlying mechanism of polymorphic ventricular tachycardia in rabbits exposed to cesium chloride, using simultaneous recordings of surface electrocardiograms and left ventricular monophasic action potentials[10]. In the present study, the prolongation of the RR interval produced an increased amplitude of the subsequent U wave (slow wave) associated with PVBs from near the peak of the U wave. PVB occurring on the markedly increased U wave triggered the episode of torsades de pointes. These characteristics of the U waves observed here are consistent with those of EADs previously reported[8-10].

In the present study, potassium supplements effectively suppressed torsades de pointes in patients with hypopotassemia. Atropine was effective in one patient with complete A-V block, perhaps by increasing the heart rate. Lidocaine or verapamil was effective in some patients. Ventricular pacing also prevented the occurrence of torsades de pointes in one patient with complete A-V block. However, direct current cardioversion was only transiently effective. The efficacy of treatments used for 7 patients were generally consistent with previous observations[2,4]. Magnesium infusion was reportedly effective treatment for torsades de pointes[11,12]. More recently, we found that nicorandil, a coronary vasodilator, was effective in suppressing EADs and ventricular tachyarrhythmias induced by cesium chloride in rabbits[10]. EADs have been induced in various conditions which increase inward current or reduced outward current (e.g., cathecolamine, low K concentrations, hypoxia, quinidine and cesium chloride)[2,3]. We attributed the suppression of EADs by nicorandil to the increase of K conductance of the cardiac membrane caused by this drug[10]. These findings suggest that a K channel activator such

as nicorandil might be an effective antiarrhythmic drug for suppressing torsades de pointes[10,13]. Our clinical studies using 24-hour ambulatory ECG recordings showed that oral nicorandil suppressed PVBs which occurred predominantly at the low heart rates[14].

要　約

抗不整脈剤によらない torsades de pointes の7例

大分医科大学　臨床検査医学
*同　内科第一
高橋尚彦，伊東盛夫，井上年夫，幸松晃正，竹下　泰*，妻夫木茂*，田村雅道*，井上　健*，前田利裕*，犀川哲典*

抗不整脈剤の投与によらない後天性 QT 延長症候群7例について，その臨床所見と torsades de pointes (TdP) の心電図学的特徴を検討した．7例に計43回の TdP 発作を記録した．4例に低カリウム血症を，また4例に TdP 発症直前の徐脈 (≦52 beats/min) を認めた．TdP 発症直前の QTc 間隔は非発作時に比し有意に延長していた (0.69±0.10 vs 0.56±0.10 sec, $p<0.05$)．TdP の心室 rate は平均 192±24 beats/min であった．計43回の TdP のすべてに "long-short initiating cycle" を，42回に "R on T (U)" 現象を認めた．TdP 発症直前に，T 波の下降脚に明らかな slow wave (U 波) を5例に認めた．先行 RR 間隔の延長に伴い U 波が増高し，さらに U 波のほぼ頂点から心室性期外収縮を発生した．U 波の振幅の増大は心室性期外収縮の頻度を増し，TdP は U 波の振幅が著明に増大したとき発生した．TdP に対して直流徐細動は一過性に有効であった．Lidocaine, atropine および verapamil の静脈内投与が有効な例もあった．発症時に低カリウム血症を示した例は，カリウムの補給により TdP 発作は消失した．

以上の所見から，1) 低カリウム血症および徐脈が TdP 発生の重要な危険因子であり，2) 先行 RR 間隔の延長に伴う U 波の増高が TdP の発症に深く関与していることが示唆された．

References

1) Fontaine G, Frank R, Grosgogeat Y: Torsades de pointes: Definition and management. Mod Concepts Cardiovasc Dis **51**: 103–108, 1982
2) Jackman WM, Friday KJ, Anderson JL, Aliot EM, Clark M, Lazzara R: The long QT syndromes: A critical review, new clinical observations and a unifying hypothesis. Prog Cardiovasc Dis **16**: 115–172, 1988
3) Surawicz B: Electrophysiologic substrate of torsade de pointes: Dispersion of repolarization or early afterdepolarizations? J Am Coll Cardiol **14**: 172–184, 1989
4) Kay GN, Plumb VJ, Arciniegas JG, Henthorn RW, Waldo AL: Torsade de pointes: The long-short initiating sequence and other clinical features: Observations in 32 patients. J Am Coll Cardiol **5**: 806–817, 1983
5) Roden DM, Thompson KA, Hoffman BF, Woosley RL: Clinical features and basic mechanisms of quinidine-induced arrhythmias. J Am Coll Cardiol **8**: 73A–78A, 1986
6) Cranefield PF, Aronson RS: Torsade de pointes and other pause-induced ventricular tachycardias: The short-long-short sequence and early afterdepolarizations. PACE **11**: 670–678, 1988
7) Bazett HC: An analysis of the time-relations of electrocardiogram. Heart **7**: 353–370, 1920
8) El-Sherif N, Bekheit SS, Henkin R: Quinidine-induced long QTU interval and torsade de pointes: Role of bradycardia-dependent early afterdepolarizations. J Am Coll Cardiol **14**: 252–257, 1989
9) El-Sherif N, Zeiler RH, Craelius W, Gough WB, Henkin R: QTU prolongation and polymorphic ventricular tachyarrhythmias due to bradycardia-dependent early afterdepolarizations. Circ Res **63**: 286–305, 1988
10) Takahashi N, Ito M, Saikawa T, Arita M: Nicorandil suppresses early afterdepolarisation and ventricular arrhythmias induced by caesium chloride in rabbits in vivo. Cardiovasc Res **25**: 445–452, 1991
11) Tzivoni D, Keren A, Cohen AM, Loebel H, Zahavi I, Chenzbraun A, Stern S: Magnesium therapy for torsades de pointes. Am J Cardiol **53**: 528–530, 1984
12) Tzivoni D, Banai S, Schuger C, Benhorin J,

Keren A, Gottlieb S, Stern S: Treatment of torsade de pointes with magnesium sulfate. Circulation **77**: 392–397, 1988
13) Fish FA, Prakash C, Roden DM: Suppression of repolarization-related arrhythmias in vitro and in vivo by low-dose potassium channel activators. Circulation **82**: 1362–1369, 1990
14) Takahashi N, Ito M, Inoue T, Koumatsu K, Saikawa T, Tsumabuki S, Arita M, Fujino T, Kagiyama H, Fukumoto T: Effects of oral nicorandil on ventricular premature contractions. Therap Res **11**: 1453–1458, 1990 (in Japanese)