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CASE REPORT

Torsades de Pointes with QT prolongation related to donepezil use

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Abstract An 83-year-old female, who had a history of anterior myocardial infarction, was treated for Alzheimer's disease with donepezil. She suffered from repeated diarrhea and vomiting, and experienced syncope. She was admitted to our hospital and was diagnosed with acute colitis and syncope. On admission, her heart rate was 54 beats/min with regular rhythm. Laboratory data showed a low plasma potassium level. Electrocardiogram (ECG) showed poor R progression, ST elevation, negative T in precordial leads, and marked QT prolongation. Transthoracic echocardiogram showed the enlargement of the left atrium and aneurysmal area at the apex. Torsades de Pointes (TdP) with syncope and convulsion were confirmed on ECG monitoring twice after admission. We treated her with potassium chloride and started magnesium sulfate and lidocaine, and then added isoprenaline injection. After these treatments, her heart rate increased and we did not detect TdP again. With the aging population in Japan, prescriptions for donepezil are increasing. We have to be vigilant for syncope in patients taking donepezil, which is possibly related to QT prolongation and TdP.

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1. Introduction

Donepezil is a cholinesterase inhibitor prescribed for patients with Alzheimer's disease. With the aging society in Japan, the prescriptions for donepezil are increasing. In addition, at present, there are no alternative oral drugs to delay the progression of Alzheimer's disease in Japan. We experienced a case of Torsades de Pointes (TdP) with QT prolongation in a patient suffering from Alzheimer's disease and taking donepezil.

2. Case report

An 83-year-old female was treated for Alzheimer's disease with donepezil (Aricept®, Eisai Co. Ltd., Japan) 5 mg/day for at least 2 years by her home physician. She also had hypertension, which had been treated with bisoprolol 5 mg/day, diabetes mellitus, paroxysmal atrial fibrillation, and a history of anterior myocardial infarction (10 years previously). She suffered from repeated diarrhea and vomiting from the morning, turned pale, and finally developed syncope. Then she was brought to our hospital by an ambulance in the evening, admitted, and was diagnosed with acute colitis and syncope. She had no previous history of syncope. On admission, she was slightly obese (the height was 146 cm and the weight 56 kg). Her heart rate was 54 beats/min, regular rhythm, and blood pressure was 148/63 mmHg. The oxygen saturation was 96% in room air. She had no cardiac murmur, rales, or leg edema. Her bowel sound was sthenic, and there was frequent and much watery stool after admission.

Laboratory data showed high white blood cell count (11,900/μL), a low plasma potassium level (3.3 mEq/L), and a high plasma brain natriuretic peptide level (318.7 pg/ml). Renal and liver dysfunction was not confirmed (aspartate aminotransferase 16 IU/L, alanine aminotransferase 7 IU/L, blood urea nitrogen 17.9 mg/dL, creatinine 0.8 mg/dL). Electrocardiogram (ECG) demonstrated poor R progression, ST elevation in V1—3 leads, negative T in V2—5 leads, and QTc (corrected QT interval) prolongation (645 msec) (Figure 1A). Chest X-ray disclosed an enlarged cardiac silhouette (cardiothoracic ratio: 60%), but no lung congestion. Transthoracic echocardiography (TTE) revealed aneurysmal area at the apex. The diameter of the end-diastolic left ventricle was 42 mm, that of the end-systole 27 mm, and the ejection fraction of the left ventricle was 56%. The size of the left atrium reached 47 mm and significant valvular failure was not detected.

Ventricular premature contraction (VPC) was frequently recorded on continuous ECG monitoring just after admission. We discontinued all oral drugs and corrected hypovolemia and the abnor-

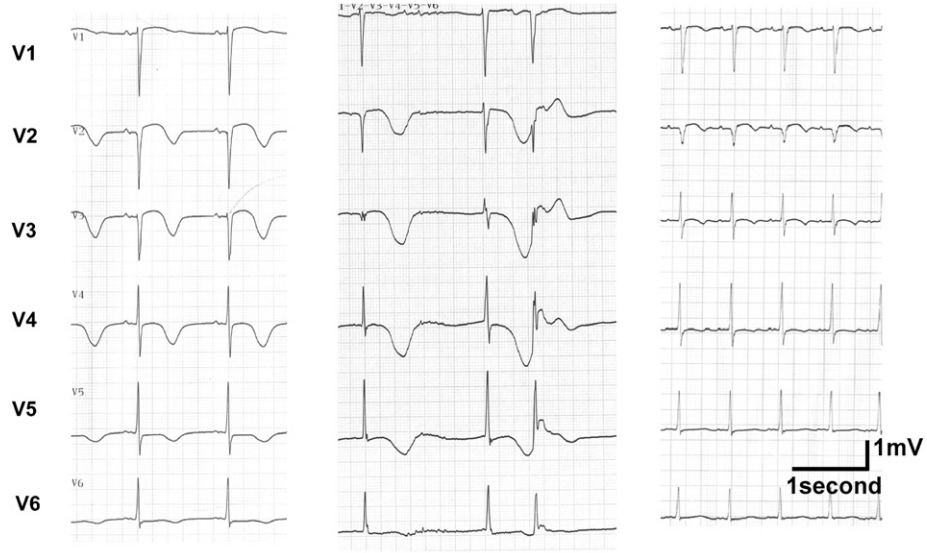

Figure 1 Changes in electrocardiogram (precordial leads). The apparent QT prolongation was detected on admission. (A) Admission, (B) next day and (C) the 14th day.

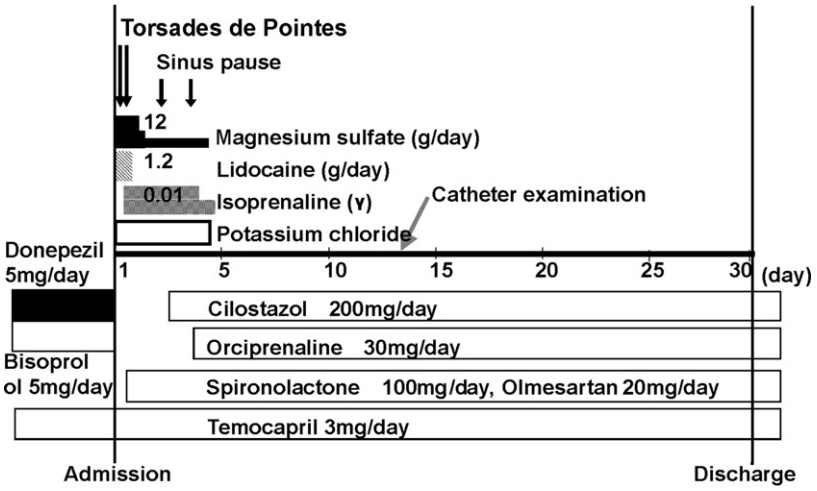

Figure 2 Clinical course of the case.

mal balance of electrolytes by intravenous injection with a potassium supplement (Figure 2). Prompt correction of plasma potassium level was, however, very difficult because of the frequent watery stool. Five hours later, we detected Torsades de Pointes for 35 s on ECG monitoring (Figure 3A), and started intravenous injection of magnesium sulfate and lidocaine (Figure 2). After an additional 5 h, at midnight, we detected TdP again with transient convulsion and syncope (Figure 3B), and discussed the use of a temporary external pacemaker. She, however, could not keep complete rest at that time, and we selected, therefore, the use of isoprenaline injection (Figure 2). After this administration, her

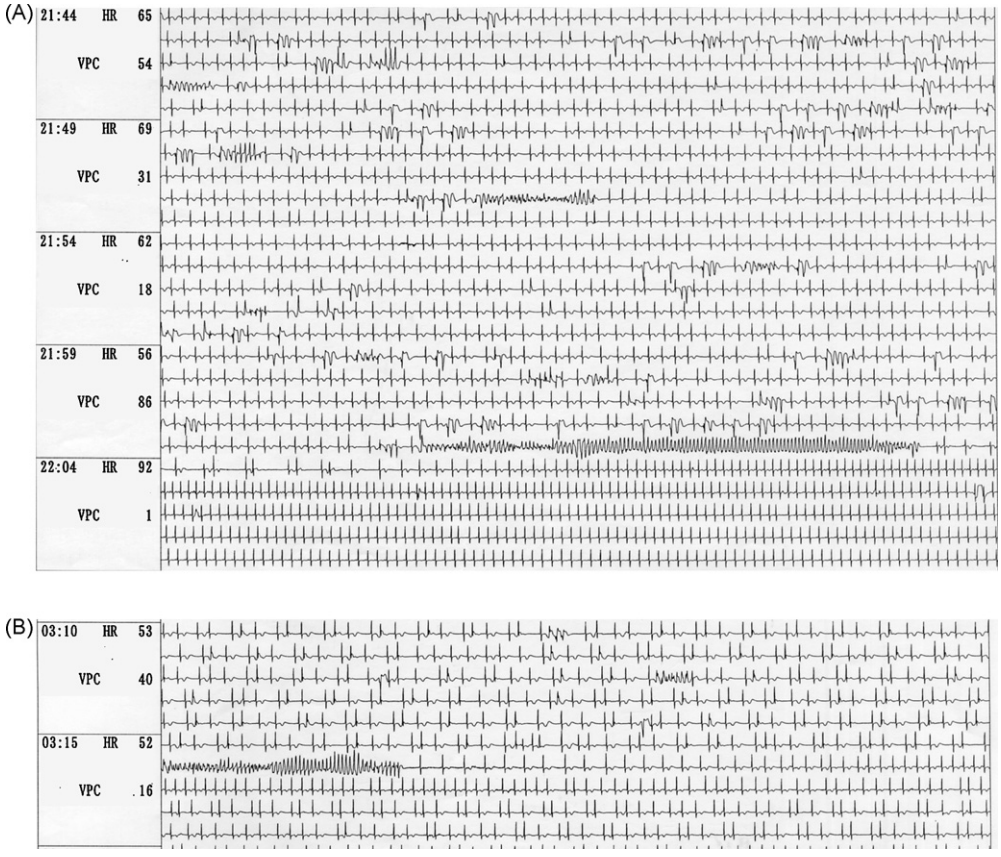

Figure 3 Continuous ECG monitoring detected Torsades de Pointes (TdP) twice. (A) 1st event (TdP sustained for 35 s) and (B) 2nd event (TdP sustained for 15 s).

mean heart rate increased to 80—90 beats/min, and the frequency of VPC decreased. We did not detect TdP again thereafter.

On the second day, her rhythm turned to atrial fibrillation and this arrhythmia terminated with a long pause (8.0 s) next day. We gradually decreased isoprenaline and changed to oral preparations of cilostazol and orciprenaline (Figure 2). We performed catheter examination on the 13th day. Coronary angiography revealed triple vessel disease. The left circumflex artery was occluded at the proximal portion and was filled with good collateral flow from the right coronary artery. The left anterior descending artery had diffuse calcified stenotic lesions from the mid to distal portion and the right coronary artery also had a mild stenotic lesion in the proximal portion. During the electrophysiological study, her rhythm turned to atrial fibrillation again by electric stimulation, and we could not evaluate the extent of conduction disorder completely. The corrected sinus recovering time was 340 msec and the HV interval was 39 msec. Three hours later, when the atrial fibrillation spontaneously terminated, we only detected a short pause on continuous ECG monitoring (2.1 s).

Discussing with the patient and her family, we selected medical follow-up considering her age, activities of daily living (ADL), and background. After washout of donepezil, we did not find worsening of dementia during admission. QTc interval in ECG gradually decreased (Figure 1C) and was 485 msec (QTc) on the fourteenth day. We adjusted her oral preparations and she was discharged in a stable condition.

3. Discussion

Donepezil is a central non-competitive reversible cholinesterase inhibitor and has been reported to be effective for all stages of Alzheimer's disease [1]. Donepezil can suppress the progression of dementia and maintain the ability of perception, cognition, global functioning, behavioral symptoms, and ADL [2]. Because of the increasing aging population, the prescriptions for donepezil are increasing. In addition, at present, there is no alternative oral preparation in Japan to delay the progression of Alzheimer's disease, which is known for its high mortality rate [3].

The frequent side effects of donepezil are appetite loss, nausea, and vomiting. In addition, donepezil is also known to cause bradycardia, sick sinus syndrome, or another arrhythmia by its cholinergic effect relating to vagal tone stimulation [4]. In some cases, discontinuation of donepezil is necessary. But, Bordier et al. [5] previously recommended the implantation of a permanent pacemaker for patients with bradycardia rather than discontinuation of donepezil, because this approach enables us to increase the dosage of donepezil. Almost all patients taking donepezil are aged people, in whom heart rate decreases with aging and the ability of handling the drug is often disturbed, and therefore often those side effects have been reported. Regarding the side effects of donepezil on cardiac rhythm, to our knowledge, there is only one report that showed a reduction of heart rate and the prolongation of PR interval, but these changes were not necessarily associated with bradycardia-induced syncope [6]. In our case, we confirmed a long pause just after the withdrawal of donepezil, which indicated that she might have potential sick sinus syndrome. This event, however, occurred during the washout period of donepezil, and we thought this bradycardia might also be related to donepezil. The half-life of donepezil in blood ranges from 70 to 100 h and we did not detect either bradycardia or TdP after the washout of the drug in this case.

It has been reported that about 3% of oral preparations are capable of prolonging QT interval [7]. TdP due to acquired QT prolongation syndrome is related to multiple factors, such as aging, female, taking beta-blocker, hypo-potassium, and baseline cardiac abnormalities such as ischemic heart disease [8]. In this case, coronary angiography revealed triple vessel disease and we thought that ischemia was likely involved in this arrhythmic event. Her plasma donepezil level on admission was 21.3 ng/ml, a slightly high level, but this level did not necessarily mean overdose (the average blood concentrations of healthy volunteers who take donepezil for 14 days: 15—20 ng/ml). Drug-induced QT prolongation syndrome did not necessarily depend on the plasma drug concentrations [8], and the mechanism was reported mainly as the blocking of potassium Ikr current, altered trafficking of proteins that form the channel, or delay of repolarization and prolongation of the consistent potential time of cardiac muscle. She might have abnormal sensitivity to donepezil or potential QT prolongation syndrome. Though Kato et al. [9] reported that donepezil did not induce QT prolongation in young volunteers, they did not evaluate the side effects associated with long-time use or those in aged patients.

Donepezil is prone to be prescribed to patients with only aging or to cases suspected of transient intensive care unit syndrome. In our case, donepezil had been prescribed since the previous admission to another hospital, and we could not fully eval-

uate the precise judgment on the indication of donepezil. After the withdrawal of donepezil, her mental state was almost stable and we could handle her dementia without donepezil. Since donepezil might cause fatal side effects, more careful attention should be paid for the induction of this drug. Although QT prolongation associated with the use of galantamine, another cholinesterase inhibitor used for Alzheimer's disease, has been shown [4], no detailed accounts on the association of TdP with the use of cholinesterase inhibitors have been reported. Our report may serve to give a warning against the easy use of a cholinesterase inhibitor for aged patients with Alzheimer's disease.

We experienced a case of TdP with QT prolongation in a patient suffering from Alzheimer's disease and taking donepezil. If patients taking donepezil experience syncope complicated with bradycardia, hypo-potassium, or ischemic heart disease, we have to pay much care to the intermittent ECG and QTc interval. That event might be due to QT prolongation and TdP.

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