CASE REPORT

Postural Orthostatic Tachycardia in a Patient with Type 2 Diabetes with Diabetic Neuropathy

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Summary

A 24-year-old Japanese man with type 2 diabetes mellitus and diabetic neuropathy was admitted to our ward to evaluate the cause of orthostatic intolerance. During a head-up tilt test, his heart rate increased from 105 to 155 beats/minute within 3 minutes, and chest discomfort began. He was diagnosed with postural orthostatic tachycardia syndrome (POTS), and orthostatic intolerance disappeared after β-blocker treatment. Scintigraphy using ^{123}I-metaiodobenzylguanidine showed decreased cardiac uptake. Power spectral analysis of heart rate variability for 24 hours in Holter electrocardiography demonstrated decreases in both sympathetic and parasympathetic nervous system activities, with a greater decrease in parasympathetic activity than sympathetic activity. The relative sympathetic hyperactivity in the present patient with diabetic neuropathy seemed to be related to POTS.

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Key words: Autonomic nervous system, Head-up tilt test, Holter electrocardiography, Orthostatic intolerance

The autonomic nervous system plays an important role in the heart's functioning.[1)] Diabetic neuropathy is one of the major complications of diabetes mellitus (DM) that involves the autonomic nervous system, as well as sensory and motor neurons.[2)] Postural orthostatic tachycardia syndrome (POTS) is a common form of chronic orthostatic intolerance that occurs on standing and is eventually relieved by lying down or sitting.[3)] The main physical finding in POTS is a dramatic increase in the heart rate (HR) on standing (> 30 beats/minute), without an appreciable decrease in blood pressure. Peripheral autonomic denervation is considered one of the mechanisms underlying POTS.[4)] The present report describes the case of a diabetic patient with diabetic neuropathy who showed POTS.

Case Report

A 24-year-old man was admitted to our ward for evaluation of the cause of orthostatic intolerance. He had been treated with insulin for type 2 DM since he was 11 years old. At 18 years, metformin was added to insulin therapy. Later, glycemic control was not good because of poor adherence to pharmacotherapy at 21 years of age. He was therefore treated with insulin therapy, achieving good glycemic control. However, he developed systemic pain about 3 months before admission and had been admitted to the Department of Neurology in our hospital, where diabetic neuropathy was diagnosed. The patient had no other notable medical history. His parents, one grandfather, and one aunt had DM. His blood pressure was 110/70 mmHg, HR was 100 beats/minute, and body mass index was 21.9 kg/m^2. A physical examination showed no abnormalities other than decreased Achilles tendon reflexes bilaterally. The chest X-ray appeared normal. Electrocardiography (ECG) showed sinus tachycardia (HR; 120/minute) without any other abnormalities. Transthoracic echocardiography demonstrated normokinesis of the left ventricle (LV), with a left ventricular ejection fraction of 58%. Laboratory data included the following: white blood cell count, 6,900/mm^3; hemoglobin, 14.0 g/dL; fasting plasma glucose, 157 g/dL; hemoglobin A1c, 8.0%; blood urea nitrogen, 11 mg/dL; creatinine, 0.52 mg/dL; total protein, 6.9 g/dL; total bilirubin, 0.5 mg/dL; aspartate aminotransferase, 9 IU/L; alanine aminotransferase, 9 IU/L; lactate dehydrogenase, 154 IU/L; creatine kinase, 51 IU/L; Na, 130 mEq/L; K, 4.4 mEq/L; Cl, 105 mEq/L; triglycerides, 145 mg/dL; low-density lipoprotein cholesterol, 94 mg/dL; high-density lipoprotein cholesterol, 57 mg/dL; uric acid, 5.9 mg/dL; C-reactive protein, 0.01 mg/dL; N-terminal pro-brain natriuretic peptide, 11.6 pg/mL; c-peptide, 0.74 ng/mL; anti-glutamic acid decarboxylase

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antibody, negative; anti-insulinoma-associated protein-2 antibody, negative; epinephrine, 15 pg/mL; norepinephrine, 189 pg/mL; dopamine, 8 pg/mL; urine protein, 2+; urine sugar, 1+; and urine albumin, 478.1 mg/mL. The thyroid function was also normal (free T_3, 3.48 pg/mL; free T_4, 1.57 ng/dL; and TSH, 1.610 μIU/mL).

Myocardial scintigraphy using ^{123}I-metaiodobenzylguanidine (MIBG) demonstrated a decreased uptake (heart-to-mediastinum ratio, 1.49; normal, 2.0-3.0) in the LV, which indicated a decrease in sympathetic innervation of the LV (Figure 1). Holter ECG showed no apparent arrhythmia, but the patient showed sinus tachycardia (HR, 85-150 beats/minute; mean, 110 beats/minute), with a total daily HR of 155,601 beats/day. Power spectral analysis of HR variability for 24 hours on Holter ECG demonstrated decreases in both sympathetic nervous system activity (low-frequency power (LF)/high-frequency power (HF), 1.76; normal, 2.46 ± 0.1) and parasympathetic nervous system activity (HF, 8.46 ms^2; normal, 862 ± 108.7 ms^2), with a more severe decrease in parasympathetic nervous system activity than in sympathetic nervous system activity (HF about 0.01 of normal value (8.46/862) versus LF/HF about 0.72 of normal value (1.76/2.46)).

To evaluate his condition, the head-up tilt test was performed. Within 3 minutes after starting the test, the patient's HR increased from 105 to 155 beats/minute in the supine position (Figure 2A), and he reported chest discomfort. His blood pressure decreased from 114/70 to 99/60 during the test, but was not sufficient to diagnose orthostatic hypotension. On cessation of the test after 30 minutes, his HR recovered to pre-test levels (Figure 2A), and symptoms disappeared. The diagnosis was POTS, and propranolol was started at a dose of 10 mg t.i.d., and increased gradually to 30 mg t.i.d. over the course of 1 week. Orthostatic intolerance subsequently resolved. The head-up tilt test was performed again after titration of propranolol to 30 mg t.i.d. His HR was seen to increase from 78 to 99 beats/minute after starting the test, with neither symptoms nor a significant decrease in blood pressure (122/64 to 108/60 mmHg) (Figure 2B). This result confirmed that propranolol was effective for POTS in this patient. At the time of writing, the patient has maintained a good condition for 3 years.

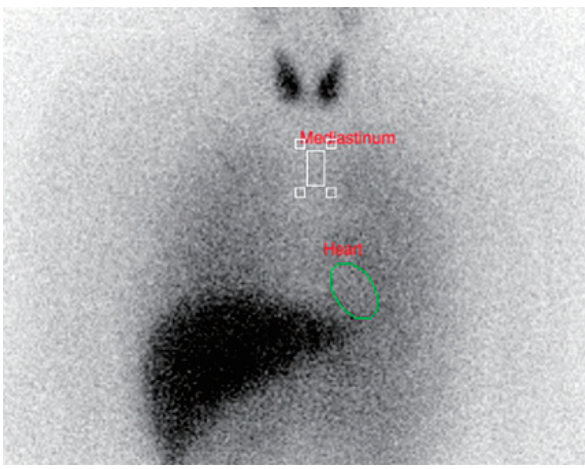

Figure 1. On ^{123}I-MIBG myocardial scintigraphy, the heart-to-mediastinum ratio is 1.49 (normal, 2.0-3.0).

Discussion

Cardiovascular autonomic neuropathy (CAN) is clinically important as a diabetic autonomic neuropathy, and results in abnormalities of HR control and vascular dynamics.[5] The major clinical manifestations of CAN include resting tachycardia, exercise intolerance, orthostatic hypotension, and silent myocardial ischemia.[6]

POTS is a heterogeneous and multifactorial disorder. Although the precise mechanisms underlying POTS are yet to be elucidated, several pathophysiological mechanisms have been proposed, including impaired sympathetic-mediated vasoconstriction in the lower limbs (neuropathic), excessive cardiac sympathoexcitatory responses, volume dysregulation, and physical deconditioning.[7] Only two previous case reports of POTS in DM have been described,[8,9] both involving young patients (a 15-year-old boy and a 19-year-old girl) with type I diabetes. One had a family history of POTS and no evidence of peripheral neuropathy, suggesting a primary genetic pathogenesis potentially exacerbated by POTS. Another patient showed POTS after traumatic stress, suggesting that central sympathetic activation following traumatic stress resulted in a disturbance in neural HR control due to a central altera-

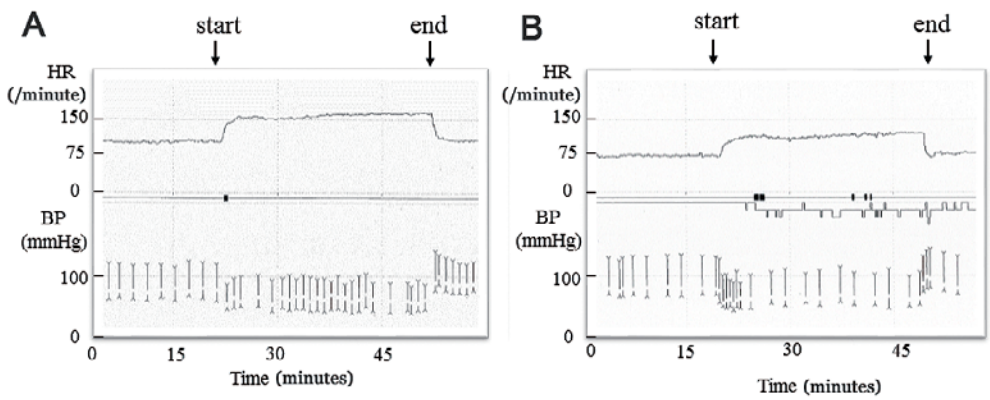

Figure 2. Head-up tilt test. **A:** Before treatment; **B:** after treatment.

tion in autonomic balance. Whether DM neuropathy itself is really related to POTS in these previous cases thus remains unclear. However, our patient had diabetic neuropathy, no family history of POTS, and no evidence of traumatic stress that could have induced autonomic imbalances.

In our patient with diabetic neuropathy, autonomic nervous system activity was shown to be decreased, and decreases in parasympathetic nerve activity were more severe than those in sympathetic nerve activity according to power spectral analysis of HR variability according to the 24-hour Holter ECG, although ^{123}I-MIBG myocardial scintigraphy showed decreased sympathetic innervation of the heart. Moreover, β-blockers proved effective against POTS in our patient. Raji et al.[10] demonstrated that the low-dose oral intake of propranolol decreased tachycardia and improved symptoms in patients with POTS, although high-dose propranolol did not improve and may worsen the condition. We successfully treated the present patients with low-dose propranolol (30 mg t.i.d.). Thus, low-dose propranolol may be enough to suppress the decreased sympathetic nervous system in our patient with diabetes. These findings suggested that relative sympathetic hyperactivity may play a pivotal role in POTS in the present patient. However, the precise mechanism of relative sympathetic hyperactivity is unclear in our patient. Previous studies demonstrated that parasympathetic neuropathy precedes sympathetic neuropathy in type 2 DM and parasympathetic nerve damage seemed to be more advanced than sympathetic damage.[11,12] Thus, a relatively early phase of neuropathy before complete, severe neuropathy that is mainly associated with orthostatic hypotension may be one of the important factors in the occurrence of POTS in DM.

In conclusion, we have to consider both POTS and orthostatic hypotension in patients with DM with orthostatic intolerance, even if ^{123}I-MIBG myocardial scintigraphy shows decreased sympathetic innervation of the heart.

Disclosures

Conflicts of interest: None.

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