INTERNAL MEDICINE

□ CASE REPORT □

An Impaired Awareness of Hypoglycemia Improved After Vitamin B_{12} Treatment in a Type 1 Diabetic Patient

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Abstract

An impaired awareness of hypoglycemia is a serious problem in diabetic patients, which can lead to life-threatening severe hypoglycemia. Recurrent hypoglycemia attenuates the function of the central, mainly hypothalamic, nervous system and it causes an impaired awareness of hypoglycemia. Vitamin B_{12} deficiency is also associated with the dysfunction of central nervous system. We report a 72-year-old type 1 diabetic patient with vitamin B_{12} deficiency whose impaired awareness of hypoglycemia improved after 4 weeks of vitamin B_{12} administration with an increased counter-hormone secretion in response to hypoglycemia. We should recognize vitamin B_{12} deficiency as one of the causes of an impaired awareness of hypoglycemia in diabetic patients.

Key words: impaired awareness of hypoglycemia, vitamin B_{12}, type 1 diabetes, central nervous system, counter-regulatory hormone

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Introduction

An impaired awareness of hypoglycemia is a status characterized by a reduced ability to perceive the onset of hypoglycemia and it is associated with a sixfold increased risk of severe hypoglycemia (1), which is a life-threatening event requiring another person's assistance to restore the blood glucose levels. An impaired awareness of hypoglycemia is caused by recurrent hypoglycemia. In diabetic patients, there is a risk for frequent hypoglycemia due to therapeutic intervention and a deteriorated glucagon secretion in response to hypoglycemia (2), which might result in more frequent hypoglycemia compared with non-diabetic patients. Recurrent hypoglycemia attenuates counter-regulatory responses to subsequent hypoglycemia (3); it is called hypoglycemia-associated autonomic failure (HAAF). Though the mechanism of HAAF has not yet been determined, it is considered that hypoglycemia attenuates the function of the central, mainly hypothalamic, nervous system (3). In general, the strict avoidance of hypoglycemia can improve an impaired awareness of hypoglycemia (4).

A vitamin B_{12} deficiency has been reported to be associated with the dysfunction of the central nervous system (5), in which vitamin B_{12} acts as a coenzyme in the methyl malonyl-CoA mutase reaction, thus leading to myelin syntheses. The neurological dysfunctions associated with vitamin B_{12} deficiency also include peripheral neuropathy, cognitive dysfunction and autonomic failure (5). Vitamin B_{12} deficiency is caused by a poor dietary intake or malabsorption derived from gastritis, gastrectomy and the use of gastric acid secretion inhibitors (6). In type 1 diabetic patients, the prevalence of autoimmune gastritis is higher than that in nondiabetic subjects (7). In addition, vitamin B_{12} deficiency can also occur in older adults (8).

We herein report an aged type 1 diabetic patient with vitamin B_{12} deficiency whose impaired awareness of hypoglycemia improved after vitamin B_{12} replacement therapy with

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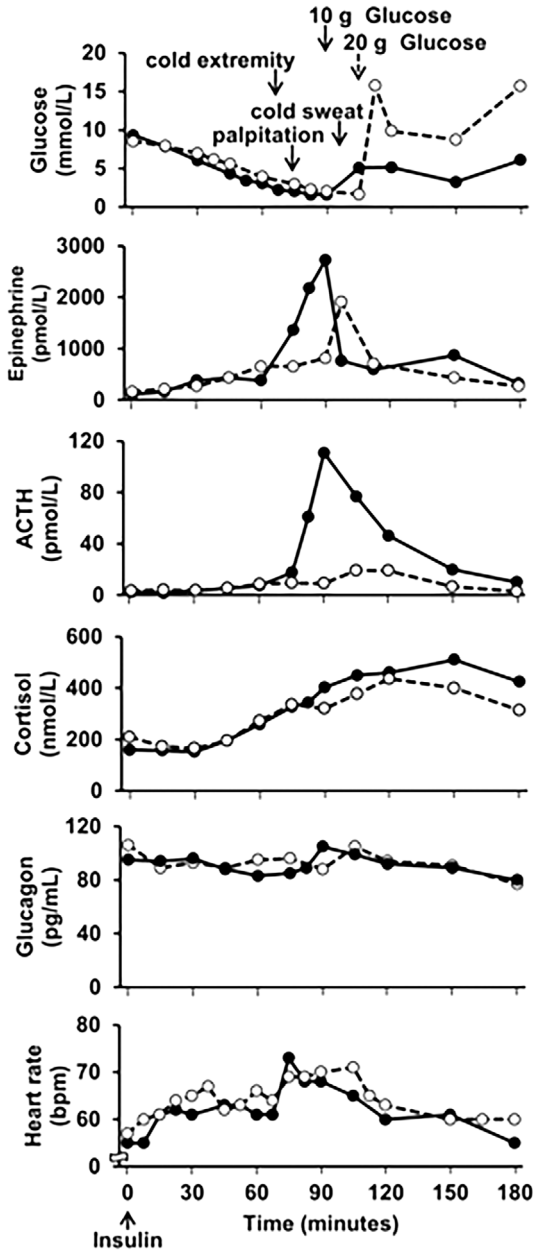

Figure. The patient's profiles of glucose, epinephrine, ACTH, cortisol and glucagon levels and heart rate in the insulin tolerance tests before (white circles, dashed line) and after (black circles, solid line) vitamin B_{12} administration.

an increased counter-hormone secretion in response to hypoglycemia.

Case Report

A 72-year-old man with type 1 diabetes was admitted to our hospital for recurrent severe hypoglycemia that tended to occur twice a month. At 31 years of age, he had undergone a subtotal gastrectomy for a gastric ulcer and had been treated with gastric acid secretion inhibitors. He suffered from type 1 diabetes since the age of 44; he had been unaware of hypoglycemia soon after its onset, which resulted in recurring hypoglycemic comas. At 71 years of age, he was admitted to our hospital, and his insulin dosage was titrated to reduce the frequency of hypoglycemia. However, his impaired awareness of hypoglycemia did not improve. Upon admission, his hemoglobin A1c level was 8.0% (64 mmol/mol). He had been suffering from chronic constipation, and his coefficient of variation of R-R interval was as low as 1.76%, suggesting that he had autonomic dysfunction. Furthermore, he was diagnosed with mild dementia by the Alzheimer's Disease Assessment Scale-Cognitive subscale (24.3; normal <20). The screening for the cause of dementia revealed a low serum vitamin B_{12} concentration (132 pg/mL; range 177-1,037) and an elevated serum homocysteine level (15.7 nmol/mL; range 3.7-13.5). Both his antigastric parietal cell antibody and anti-intrinsic factor antibody were negative, and he had not been treated with biguanide. His vitamin B_{12} deficiency was thought to result from the combination of gastrectomy, the use of gastric acid secretion inhibitors, and his advanced age. Thus, we considered that central nervous dysfunction due to vitamin B_{12} deficiency might have affected the impaired awareness of hypoglycemia in this patient.

He was treated by a daily intramuscular injection of 1,000 μg of vitamin B_{12} for 2 weeks and then by the daily oral administration of 1,500 μg of vitamin B_{12}. For an evaluation of the counter-regulatory hormone secretion in response to hypoglycemia, an insulin tolerance test (ITT) was done. We obtained informed consent for performing ITT from the patient and his daughter. The ITT before vitamin B_{12} administration revealed that he was unaware of hypoglycemia despite low serum glucose levels (1.7 mmol/L). In an ITT 4 weeks after vitamin B_{12} administration (vitamin B_{12}; 3,150 pg/mL, homocysteine; 6.7 nmol/mL), he demonstrated some symptoms of hypoglycemia (e.g., cold extremities, palpitation and cold sweats), when the lowest serum glucose level reached almost the same as the previous one (1.6 mmol/L) (Figure). The plasma epinephrine response level to hypoglycemia increased from 1,910 to 2,730 pmol/L, and the plasma adrenocorticotropic hormone (ACTH) and serum cortisol levels also increased from 20 to 111 pmol/L and from 440 to 510 nmol/L, respectively (Figure). Along with his increased epinephrine levels, there was also an increase in the heart rate (Figure). The increase in the glucagon levels in response to hypoglycemia deteriorated in ITT and it did not improve after vitamin B_{12} administration (Figure). The patient's coefficient of variation of R-R interval increased from 1.76 to 2.33%, and his Alzheimer's disease Assessment Scale-Cognitive subscale score decreased from 24.3 to 12.7, suggesting that both his peripheral autonomic dysfunction and cognitive dysfunction had improved. After he was discharged from the hospital, he began to feel slightly uncomfortable when hypoglycemia occurred and he has since experienced only one episode of hypoglycemic coma in the nearly 8-month follow-up period.

Discussion

Our report describes the first case of type 1 diabetes com-

plicated with vitamin B_{12} deficiency whose impaired awareness of hypoglycemia improved with an increased counter-regulatory hormone secretion, except for glucagon secretion, after 4 weeks of vitamin B_{12} administration. An impaired awareness of hypoglycemia is caused by a dysfunction of the central, mainly hypothalamic, nervous system in humans (3). The higher increase in the plasma ACTH levels in an ITT after vitamin B_{12} administration might partly reflect the amelioration of hypothalamic dysfunction in this case. In vitamin B_{12}-deficient rats, the hypothalamic abnormalities with glial fibrillary acidic protein and myelin basic protein mRNA decreases improved after its replacement therapy (9).

Both the cognitive and autonomic dysfunction also improved in this case. There have been several reports that cognitive impairment is occasionally reversible after B_{12} replacement therapy in patients with vitamin B_{12} deficiency (10-13). In another report, a patient with vitamin B_{12} deficiency and autonomic dysfunction of orthostatic hypotension, improved after 2 weeks of treatment with vitamin B_{12} (14). It was a limitation, however, that strict avoidance of hypoglycemia in this patient during hospitalization might have partly improved his impaired awareness of hypoglycemia.

In conclusion, we should recognize vitamin B_{12} deficiency as one of the causes of central nervous system dysfunction and peripheral autonomic dysfunction, and the potential effectiveness of vitamin B_{12} replacement therapy for improving the awareness of hypoglycemia in diabetic patients.

The authors state that they have no Conflict of Interest (COI).

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S.F., T.K. and J.K. were the attending physicians of this patient and wrote the manuscript. A.I. contributed to the discussion and reviewed and edited the manuscript. C.I., T.K., K.F., T.Y., H. I. and I.S. contributed to the discussion. A.I. is the guarantor of this work and thus had full access to all of the study data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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