OBSERVATIONS

Repeated Hypoglycemia Caused by the Overproduction of Anti-insulin Antibodies and Isolated ACTH Deficiency in a Type 2 Diabetic Patient Receiving Insulin Therapy

A 46-year-old man with untreated type 2 diabetes visited our hospital. His plasma glucose and HbA_{1c} levels were 429 mg/dL and 11.5%, respectively. He had no renal dysfunction. Insulin therapy (18 units aspart and 22 units biphasic insulin aspart 30/70) was initiated, and the HbA_{1c} level improved (5.7–6.4%). One year later, he started experiencing frequent hypoglycemic attacks, which persisted despite significantly reducing his insulin dosage (total 9 units). Fasting plasma glucose, serum immunoreactive insulin (IRI), C-peptide, and HbA_{1c} levels were 75 mg/dL, 420 μU/mL (reference, 1.7–10.4), 1.2 ng/mL (reference, 0.6–1.8), and 5.4%, respectively. His anti-insulin immunoglobulin G antibody (IA) titer (125I-insulin binding rate) was 95.5% (reference, 0–7.0); free and total IRI levels were 11.0 and >240 μU/mL, respectively. After insulin cessation, nocturnal hypoglycemia persisted (28–50 mg/dL).

In addition, his serum sodium level gradually decreased in the past 2 months (from 142 to 128 mmol/L [reference, 138–146]). Adrenal function was evaluated: plasma ACTH and cortisol levels at 0700 and 2300 h were 21.0 pg/mL (reference, 7.4–54.7) and 2.3 μg/dL (reference, 4.0–18.3), and 11.0 pg/mL and <1.0 μg/dL, respectively. His 24-h urinary free cortisol level was 6.5 μg (reference, 11.2–80.3). Corticotropin-releasing hormone (100 μg i.v.) test revealed blunted responses of plasma ACTH and cortisol levels (20.0–23.0 pg/mL and 1.4–1.9 μg/dL, respectively). His basal levels of growth hormone, gonadotropins, thyrotropin, and prolactin, and their responsiveness to growth hormone-, gonadotropin-, and thyrotropin-releasing hormones were almost normal. Magnetic resonance imaging revealed a normal pituitary gland. These observations indicated a recent-onset isolated ACTH deficiency (IAD).

Replacement with 15-mg hydrocortisone normalized the 24-h urinary free cortisol level (24.8 μg) and improved hyponatremia. Since diurnal hyperglycemia remained, 90-mg nateglinide was initiated and increased to 270 mg. Frequency of hypoglycemia gradually decreased. The IA titers and IRI levels were 62.7% and 57.3 μU/mL, 47.9% and 12.2 μU/mL, and 15.3% and 7.9 μU/mL after 5, 7, and 11 months, respectively. HbA_{1c} level was 5.7–6.3% without hypoglycemia. The HLA haplotype was *DRB1*090102/150201–DQB1*030302/060101*. The *DRB1*0406* allele was undetectable, which is common in Japanese patients with insulin autoimmune syndrome (1).

An excessive production of IAs against exogenous insulin causes unexpected hypoglycemia (2). In this patient, a high titer of IAs and IAD occurred almost simultaneously after 1 year of insulin treatment, resulting in recurrent hypoglycemia. An accurate diagnosis was important to initiate appropriate treatment; glucocorticoid supplementation and nateglinide substitution for insulin reduced the IA titers. This clinical course suggests that endogenous glucocorticoid prevented the overproduction of IAs before the onset of IAD. Although the IAD was idiopathic, an immune rebound mechanism due to adrenal deficiency might have triggered IA production, since acute changes in cortisol levels have been reported to cause autoimmune diseases (3,4). Pharmacological doses of glucocorticoids often decrease IA titers in insulin-treated diabetic patients (5). Conversely, the overproduction of IAs in the absence of glucocorticoids has not been reported. This rare case suggests that an imbalance between endogenous glucocorticoid levels and the immune system induces overproduction of IAs.

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