Insulin Glulisine May Cause a Disease Resembling Insulin Autoimmune Syndrome: Case Report

Insulin autoimmune syndrome (IAS) is a rare cause of spontaneous hypoglycemia with severe hyperinsulinemia characterized by high titers of insulin antibodies (IAs) without prior insulin injections (1). Whereas IAs is usually caused by drugs containing sulfhydryl compounds or α-lipoic acid (2), we report a disease resembling IAS, possibly induced by insulin glulisine.

A 71-year-old man was diagnosed with type 2 diabetes at 62 years of age in 2003. While he was treated with glimepiride from 2009, his glycemic control remained poor. In February 2011, he repeatedly suffered nocturnal hypoglycemia along with daytime hyperglycemia. Although glargine was discontinued in July 2011, nocturnal hypoglycemia continued to occur. Therefore, he was admitted to our hospital in May 2012.

When three daily glulisine injections (0.52 units/kg/day) were continued after admission, his plasma glucose level fell from 400–500 mg/dL at midnight to <50 mg/dL by 7:00 A.M., together with daytime hyperglycemia (300–400 mg/dL). Fasting blood samples revealed a plasma glucose level of 50 mg/dL, immunoreactive insulin level of >1,000 μIU/mL, C-peptide level of 2.9 ng/dL, and high titer of IA (>50 units/mL [normal range <0.4 units/mL]). Scatchard analysis revealed low-affinity/high-binding capacity against human insulin for high-affinity sites of IA (Fig. 1A), almost equivalent to values reported in typical IAS cases (3), indicating IAS-like pathophysiological features.

When glulisine was switched to lispro, daytime hyperglycemia promptly improved (100–150 mg/dL) during the next few days together with disappearance of nocturnal hypoglycemia, indicating that the IA might have high-affinity/low-binding capacity against lispro. The insulin requirement was finally reduced to 0.17 units/kg/day. Intriguingly, 6 months after the switch, serum immunoreactive insulin level had dropped to 126 μIU/mL, even though the titer of IA remained high (>50 units/mL), indicating a favorable change in the features of the IA. Indeed, his IA shifted to having higher-affinity/much lower binding capacity than his initial IA (Fig. 1B), resembling common IA seen in insulin-treated diabetic patients (3). These findings suggest that glulisine might have been immunologically perceived as a target antigen, associated with the development of IAS-like pathophysiological features.

Insulin analogs have an amino acid sequence that differs from that of human insulin, so they are believed to be recognizable as non–self-antigens. Moreover, insulin aggregation mediated by zinc may affect immunogenic potential owing to the longer residence of aggregates at the injection site and easy uptake by antigen-presenting cells (4). Because glulisine exists as monomers or dimers in solution without zinc, and can be rapidly absorbed into the bloodstream after subcutaneous injection, it is considered to be less immunogenic than other insulin products (5). Thus, it is hard to infer the immunological mechanism of IAS-like pathophysiological features caused by glulisine. Presumably, individual variability in immunoreactivity unique to glulisine might be involved as a genetic predisposition. Physicians should consider the possibility that glulisine may contribute to the development of diseases resembling IAS.

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Figure 1—Scatchard analysis of IAs using 125I-human insulin. Serum, with insulin removed by dextran-coated charcoal, was used for analysis. A: Scatchard analysis performed just before switch from glulisine to lispro (white circles, broken lines). At this point, the patient had polyclonal IAs with K1 of 0.0740 × 10^9 M^-1 and b1 of 26.0 × 10^-8 M. B: Scatchard analysis was performed ~6 months after switch from glulisine to lispro (black circles, solid lines). At this point, the patient had polyclonal IAs with K1 of 0.282 × 10^9 M^-1 and b1 of 1.94 × 10^-8 M. The inset shows the enlarged figure of B. «B», concentration of bound insulin; B/F: bound/free insulin ratio; K1 and b1, affinity constant and binding capacity, respectively, for high-affinity sites of IAs; M, mol/L.
and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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