Hyperinsulinemic hypoglycemia associated with insulin antibodies caused by exogenous insulin analog

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Summary

Insulin antibodies (IA) associated with exogenous insulin administration seldom caused hypoglycemia and had different characteristics from insulin autoantibodies (IAA) found in insulin autoimmune syndrome (IAS), which was first described by Dr Hirata in 1970. The characteristic of IAS is the presence of insulin-binding autoantibodies and related fasting or late postprandial hypoglycemia. Here, we report a patient with type 1 diabetes mellitus under insulin glargine and insulin aspart treatment who developed recurrent spontaneous post-absorptive hyperinsulinemic hypoglycemia with the cause probably being insulin antibodies induced by exogenous injected insulin. Examinations of serial sera disclosed a high titre of insulin antibodies (33%, normal <5%), high insulin concentration (111.9 IU/mL) and undetectable C-peptide when hypoglycemia occurred. An oral glucose tolerance test revealed persistent high serum levels of total insulin and undetectable C-peptide. Image studies of the pancreas were unremarkable, which excluded the diagnosis of insulinoma. The patient does not take any of the medications containing sulfhydryl compounds, which had been reported to cause IAS. After administering oral prednisolone for 3 weeks, hypoglycemic episodes markedly improved, and he was discharged smoothly.

Learning points:

- Insulin autoimmune syndrome (IAS) or IAS-like situation should be one of the differential diagnosis in patients with hyperinsulinemic hypoglycemia.
- Although less reported, insulin antibodies (IA) caused by exogenous insulin analog should be considered as the cause of hypoglycemia.
- Patients with suspected insulin autoimmune syndrome (IAS) should be screened for drugs related to autoimmunity to endogenous insulin.

Background

Hyperinsulinemic hypoglycemia can be caused by exogenous or endogenous insulin action. As a gold standard test for hypoglycemia, prolonged fast test helps to confirm the presence of inappropriate insulin secretion when hypoglycemia developed. The differential diagnosis of hyperinsulinemic hypoglycemia included insulin injection, sulfonylurea drug, insulinoma, nesidioblastosis and insulin autoantibodies (IAA)-related insulin autoimmune syndrome (IAS). Insulin autoimmune syndrome (IAS), which is characterized by a high concentration of total serum immune-reactive insulin (IRI) and circulating insulin autoantibodies (IAA) during

hypoglycemia, should be considered after excluding insulinoma and nesidioblastosis (1, 2, 3). Patients with IAS often have underlying autoimmune disorders or have been exposed to certain drugs containing a sulfhydryl group, such as methimazole. In rare cases, insulin antibodies (IA) associated with exogenous insulin administration caused hypoglycemia. Insulin antibodies (IA) are often seen in patients receiving insulin treatment. These insulin antibodies (IA), which typically had low capacity and high affinity rarely cause hypoglycemia, which are unlike the high-capacity and low-affinity characteristics of IAA presented in IAS (3, 4). Herein is a rare case of IA-related recurrent severe hypoglycemic coma probably associated with exogenous insulin analogs, which had similar clinical presentation as IAS.

Case presentation

A 48-year-old man was admitted to our hospital with recurrent severe hypoglycemic coma. His history included type 1 diabetes mellitus for 20 years, receiving multiple-dose insulin injection. Initially, he received Humulin R and Humulin N injection with total daily dose about 40 units. He started to use insulin aspart plus insulin glargine since 4 years ago and latest hemoglobin A1c was 7.6%. Frequent hypoglycemia and syncope events were noted for 1 year. At first, hypoglycemic coma happened about twice annually, but the frequency increased to 3 times a week in recent months. In the past three months, the patient repetitively suffered from unconsciousness and was sent to the emergency department of hospitals nearby where severe hypoglycemia below 30 mg/dL was noted. He was referred to our hospital for further survey of etiology of hypoglycemia. During hospitalization, several episodes of disturbed consciousness due to hypoglycemia recurred. Clinically, the patient had clear consciousness most of the time but looked chronically ill, with a body weight of 54 kg. He denied an exposure history to a sulfhydryl drugs, such as methimazole.

Investigation

On physical examination, his body height was 163 cm, weighed 54 kg and body mass index was 20, others disclosed no significant finding. Blood cell counts and biochemical data were unremarkable.

During one episode of disturbed consciousness, the following values were recorded: serum glucose concentration: 34 mg/dL; insulin (IRI): 61.1 IU/mL; C-peptide <0.01 ng/mL. The patient was euthyroid with

thyroid-stimulating hormone (TSH) level of 0.32 IU/mL and free T4 level of 0.92 IU/mL. For survey of adrenal insufficiency, the 08:00h serum cortisol level was 11.1 µg/dL. Due to high insulin but low C-peptide level, factitious disorder was first suspected. We had ensured that he did not self-administrate insulin during hospitalization by frequent visits by nurses especially during sleep time.

Physician-attended prolonged fast test was performed, and hypoglycemia episode developed soon after 4 h with hyperinsulinemia with the following values: serum glucose concentration: 38 mg/dL; insulin (IRI): 111.9 IU/mL and C-peptide: <0.01 ng/mL. These findings were consistent with hyperinsulinemic hypoglycemia. In addition, an unusually high level of insulin antibodies (33%; normal, <5%) was identified in the patient's serum. Computed tomography of the abdomen was negative.

Capillary blood glucose concentrations were monitored before meals, before bed time and at 03:00h to study the pattern of hypoglycemia in the patient. A 24-h blood glucose profile revealed a fasting hypoglycemia, with a nadir frequently occurring at around 05:00–06:00h of a day (Fig. 1). To further define the relationship between the serum concentrations of glucose and total insulin, an oral glucose tolerance test was performed. After a 75 g glucose load, total insulin level increased markedly at 30 min, but it was kept in high level greater than 80 IU/mL. At the time point of 5 h, hypoglycemia with blood glucose of 45 mg/dL and a simultaneous insulin level of 97.9 IU/mL were recorded, which indicated post-absorptive hyperinsulinemic hypoglycemia (Fig. 2).

Treatment

Insulin regimens were shifted from insulin aspart plus insulin glargine to Humulin N and Humulin R 2 days after admission. However, the severity and frequency of
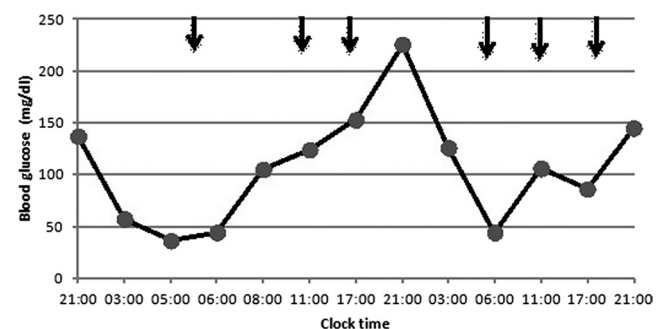
Figure 1
A 48-h blood glucose profile revealed early morning hypoglycemia. Black arrows indicate meal ingestion.
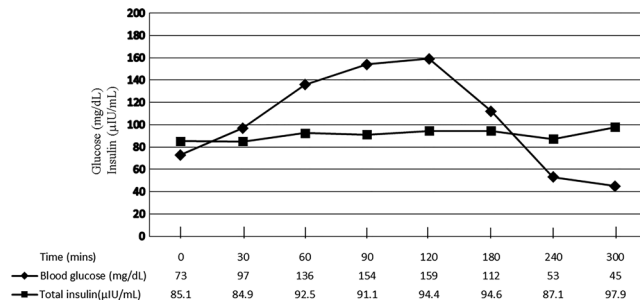
Figure 2
After a 75 g glucose load, total insulin remained in high level until 5 h, indicating a relatively delayed clearance. At 5 h after load, blood glucose 45 mg/dL with insulin 97.9 IU/mL. Glucose (solid diamonds) and total insulin (solid squares).

hypoglycemia events did not improve. Prednisolone was then administered one week later with the dosage of 30 mg per day for the following 3 weeks during hospitalization.

Outcome and follow-up

After administering oral prednisolone 30 mg per day, the severity and frequency of hypoglycemia events improved in one week. The time of nadir blood glucose level during a day is more predictably with hypoglycemia frequency decreased from once or twice a day to twice a week during the following weeks. It usually happened around 3 o'clock to 6 o'clock in early morning with a glucose level greater than 60 mg/dL. No liable glucose control was noted after prednisolone treatment by blood glucose monitoring 4 times a day. We kept his insulin regimen with multiple dose injection of Humulin R and Humulin N during this period. He was then discharged smoothly with 30 mg oral prednisolone per day.

Discussion

Insulin antibodies (IA) are not uncommon in patients receiving insulin injection. These antibodies had the characteristics of low capacity and high affinity, which seldom cause hypoglycemia or hyperglycemia (5). From the literature, incidence of 0.16% of exogenous insulin-induced insulin antibodies in patients with diabetes had been reported (6). In a study surveying 118 Japanese patients who used insulin, insulin antibodies were detected in 40.7% of them, and insulin glargine was the most antigenic (7). Insulin analog has an amino acid sequence different from human insulin, which could possibly be recognized as an antigen. On the other hand, insulin autoimmune syndrome (IAS), or Hirata disease, is a rare

cause of hyperinsulinemic hypoglycemia characterized by autoantibodies to insulin (IAA) caused by medications other than exogenous insulin (8). The antibodies seen in the disease had high capacity and low affinity and lead to hypoglycemia. It is the third leading cause of spontaneous hypoglycemia in Japan after insulinoma and extra-pancreatic neoplasms. About 400 cases have been reported in the medical literature since, with the majority (90%) depicted in the Japanese population (9). An underlying autoimmune disease or an exposure history to a sulfhydryl drug, such as methimazole, is found associated with IAS. Our patient had not taken sulfhydryl-containing drugs or other drugs reportedly associated with IAS. Tracing back his treatment of type 1 diabetic mellitus, there were four types of insulin: Humulin N, Humulin R, insulin aspart and insulin glargine. Whether the insulin antibodies are caused by insulin analogs or humulin insulin cannot be documented in these patients for the reason that he did not had the insulin antibodies checked before or during the 20 years of disease. However, according to the temporal association that hypoglycemia events became obvious after shifting to insulin analogs and the higher immunogenic effect of insulin glargine than human insulin in the literature (7), insulin analogs would be the first priority to consider. Therefore, IA induced by exogenous insulin that had the characteristics of high capacity and low affinity was the most likely cause of hypoglycemia in this patient.

In our patient, the markedly elevated levels of total insulin, low C-peptide level, high level of insulin antibodies (33%) together with the fact that total insulin remained elevated while plasma glucose began to decline during an oral glucose tolerance test, suggest a delayed clearance of insulin, apparently due to binding of released insulin by insulin-binding antibodies. The notion that the insulin–antibody complex is responsible for the development of late postprandial hypoglycemia similar to patients with IAS was introduced by Uchigata *et al*. (9). There are some case reports about IAS-like situation induced by exogenous insulin. Reported in 2014, a lean 15-year-old girl was diagnosed with type 1 diabetes based on symptomatic hyperglycemia and positive anti-islet cell antibodies required for treatment of hyperglycemia and ketosis alternating with refractory hypoglycemia after using twice-daily mixed insulin for 11 months (10). A case report of two patients who developed daytime hyperglycemia and early morning hypoglycemia because of insulin antibody (IA) with affinity lower and binding capacity higher than insulin autoantibodies (IAA) in

the insulin autoimmune syndrome (IAS) after insulin treatment being changed from human insulin to analog insulin was published in 2009 (3).

The largest case series of insulin antibody-associated immunological hypoglycemia was an 11 cases report from China (11). The conclusion is that hypoglycemia associated with insulin antibodies shall not be neglected in insulin-treated patients and if unexpectedly recurrent hypoglycemia occurred, especially after insulin had been discontinued for several days, immunological hypoglycemia associated with IA due to exogenous insulin should be considered (11). The authors concluded that prompt insulin withdrawal was needed; however, this was not possible in our patient who had type 1 diabetes mellitus. Recurrent hyperinsulinemic hypoglycemia would disappear after discontinuing drugs causing IAS (12). In patients with prolonged recurrent hyperinsulinemic hypoglycemia or unknown cause of IAS, immunosuppressive therapy may help to shorten the duration of the disease. Corticosteroid and plasmapheresis are usually the choices of immunosuppressive therapy. Unfortunately, this patient had type 1 diabetes and should be treated with multiple doses of insulin injection without cessation. Therefore, he took oral prednisolone 30 mg per day for his IAS-like situation, and a good response was observed without the deterioration of hyperglycemia by frequent blood sugar monitoring for 2 weeks in the hospital, which is similar to previous case reports (3, 13).

Mostly, the hypoglycemic episodes happened during the late postprandial period, and it was assumed that most insulin secreted from endogenous origin or administered from exogenous method was bound to antibodies and then dissolved from the complex to exert its effect, thus producing postprandial hypoglycemia (14, 15). IAS can present with fasting or post-absorptive hypoglycemia. In our patient, the hypoglycemia usually developed at early morning or post-absorptive status (Figs 1 and 2), which is consistent with typical IAS. The triggering factors that cause the dissociation of insulin and insulin antibodies are not clear.

The cause of inducing insulin antibodies (IA) is heterogeneous and remains incompletely understood. From the study of IAS, underlying autoimmune disorders, specific human leukocyte antigen (HLA) typing, sulfhydryl-containing drugs such as methimazole, thiopronin, penicillamine, glutathione and other drugs, including hydralazine, procainamide and isoniazid, have been associated with this uncommon syndrome

(8, 16, 17, 18, 19). Immunogenetic evidence suggests a striking association between polyclonal IAS and specific HLA class II antigens such as DRB1*0406, DQA1*0301 and DQB1*0302 (1, 3, 17). Further studies indicate that certain amino acids at position 74 in the HLA-DR4 β1 chain might be involved in the pathogenesis of insulin autoantibody production (17). Other factors attributed to IA production included purity and species of insulin administrated (20).

The major limitation of current case report is the lack of Scatchard plot analysis. The IA emerged from insulin analogs with high capacity and low affinity should be proven by characterizing these different clones of antibodies. The case presented here wish to raise the attention to the possibility that IA induced by exogenous insulin analogs may have the similar clinical characteristics as insulin autoantibodies (IAA) seen in IAS and should be considered in diabetes patients treated with insulin. Further, Scatchard analysis of the IA is warranted to establish the exact clones and prevalence of IA that will affect pharmacokinetics of insulin therapy.

In conclusion, IA, although uncommon clinically, should be one of the differential diagnosis in patients with hyperinsulinemic hypoglycemia. IA induced by exogenous insulin analog seldom had clinical significance but still causes hypoglycemia in our case and in few case reports which had the similar clinical effects as IAS. This should be considered in patients having type 1 diabetes mellitus with frequent hyperinsulinemia hypoglycemia

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