Severe Hypoglycemic Coma due to Insulin Autoimmune Syndrome

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Insulin autoimmune syndrome, characterized by the presence of insulin-binding autoantibodies and fasting or late postprandial hypoglycemia, is a rare cause of hypoglycemia. We report a patient with pulmonary tuberculosis who developed recurrent spontaneously post-absorptive hyperinsulinemic hypoglycemia after treatment with antituberculous drugs. Imaging studies of the pancreas were unremarkable, and selective intra-arterial calcium stimulation with hepatic venous sampling for insulin failed to show a gradient, thus almost completely excluding the possibility of occult insulinoma or nesidioblastosis. Examinations of sera, however, disclosed a high titer of polyclonal insulin-binding autoantibodies containing at least 2 classes of binding sites, 1 with high affinity but low capacity, and the other with low affinity but high capacity. An oral glucose tolerance test revealed high serum levels of total insulin associated with relatively low levels of free insulin, but not of C-peptide, suggesting binding of the released insulin to autoantibodies. Regretfully, shortly after the withdrawal of isoniazid, the patient died of respiratory failure unrelated to hypoglycemia, and whether these antibodies were induced by isoniazid remains unknown. We recommend that insulin autoimmune syndrome be one of the differential diagnoses in patients with hyperinsulinemic hypoglycemia. [*J Chin Med Assoc* 2005;68(2):82–86]

Key Words: hypoglycemia, insulin autoantibody, insulin autoimmune syndrome, isoniazid

Introduction

Hypoglycemia with concurrent hyperinsulinemia implies exogenous or endogenous insulin action related either to medications or pancreatic lesions. Prolonged fasting, the gold standard test for hypoglycemia, helps to confirm the presence of inappropriate insulin secretion from insulinoma or diffuse islet-cell hyperplasia (nesidioblastosis). Insulinoma, if present, may be localized by imaging studies, whereas a negative result does not completely exclude the possibility of occult islet-cell tumor or nesidioblastosis, in which insulin secretion can be triggered by calcium injection into the arteries supplying the tumor or the nesidiodysplastic tissue, a technique termed "selective intra-arterial calcium stimulation" testing or "arterial stimulation and venous sampling (ASVS)".[1] The detection rate of insulinoma with this localization method was reported to be about 85–90%.[1] However, spontaneous hyperinsulinemic hypoglycemia can be due to a much rarer disorder, insulin autoimmune syndrome (IAS),[2–6] which is characterized by hypoglycemia, a high concentration of total serum immunoreactive insulin (IRI), and circulating monoclonal or polyclonal insulin-binding autoantibodies. Mostly, IAS patients have either an underlying autoimmune disorder or have previously been exposed to drugs containing a sulfhydryl group, such as methimazole. Herein is a case of recurrent severe hypoglycemic coma caused by IAS after antituberculous drug therapy.

Case Report

A 76-year-old man was admitted to our hospital with recurrent severe hypoglycemic coma. His past history

included a case of chronic bronchitis, but no diabetes mellitus or treatment with insulin or oral antidiabetic drugs. Three months before admission, the patient had developed poor appetite and weight loss of approximately 10 kg within a few months. A chest X-ray taken at a local hospital disclosed ill-defined opacities in both lung fields, with more dense infiltration over the right upper lobe and bilateral basal lung regions. Pulmonary tuberculosis was proven by a positive acid-fast stain on sputum specimen. Anti-tuberculous therapy with ethambutol 400 mg twice daily and Rifater® 2 tablets twice daily (each tablet contains rifampicin 120 mg, isoniazid 80 mg and pyrazinamide 250 mg) was started. One month after taking anti-tuberculous drugs, a sudden onset of cold sweating, palpitations and loss of consciousness occurred; symptoms were relieved after intravenous glucose injection. Then, the patient was admitted to the local hospital again. During the hospitalization, several episodes of disturbed consciousness recurred and the diagnosis of hyperinsulinemic hypoglycemia was made. During 1 episode of disturbed consciousness, the following values were recorded: serum glucose concentration 19 mg/dL; insulin (IRI) 45.7 μIU/mL; and C-peptide 0.96 ng/mL. Magnetic resonance imaging of the abdomen was negative. The patient was transferred to our hospital for further evaluation.

Clinically, the patient had clear consciousness but looked chronically ill and cachectic, with a body weight of 35.3 kg. Physical examination disclosed coarse breath sounds and marked muscle wasting. Blood cell counts and biochemical data were unremarkable, except for hyponatremia (121 mmol/L), hypoalbuminemia (2.9 g/dL), and hyperglobulinemia (5.0 g/dL). The patient was euthyroid with a thyroid-stimulating hormone level of 2.99 μIU/mL (normal range, 0.4–4.0 μIU/mL) and free thyroxine level of 1.28 ng/dL (normal range, 0.8–1.9 ng/dL). Anti-thyroglobulin and anti-peroxidase antibody levels were 21 U/mL (normal range, < 60 U/mL) and 328.5 U/mL (normal range, < 60 U/mL), respectively.

Prolonged fasting was not performed, since an episode of hypoglycemia occurred again soon after admission. During this episode, a plasma glucose concentration of 35 mg/dL and simultaneous IRI level of 27.22 μIU/mL and C-peptide level of 3.22 ng/mL were noted. These findings were consistent with hyperinsulinemic hypoglycemia. The 8 a.m. serum cortisol level was 14.32 μg/dL, which rose to 19.99 μg/dL after a low-dose (5 μg) adrenocorticotropin-stimulation test, thus excluding the possibility of adrenal insufficiency. Imaging studies, including abdominal computerized tomographic scan and

pancreatic angiography, failed to detect lesions. An ASVS test, as previously described by Doppman,[1] was performed for possible occult pancreatic abnormalities. Briefly, after standard pancreatic angiography, calcium was infused into different arteries via a catheter inserted through the femoral artery, and blood samples were withdrawn from the right hepatic vein for insulin determination. The results revealed no gradient of insulin level after calcium injection into the superior mesentery artery, the gastroduodenal artery, the hepatic artery, the proximal splenic artery, or the distal splenic artery. These findings almost certainly excluded the possibility of occult insulinoma or nesidioblastosis.[7]

Plasma-protein electrophoresis revealed a low albumin level and a wide-base elevation of polyclonal gamma globulin. Plasma immunoglobulin (Ig) fractions of IgG, IgA and IgM were 2,380 mg/dL (normal range, 751–1,560 mg/dL), 673 mg/dL (normal range, 82–453 mg/dL), and 73.1 mg/dL (normal range, 46–304 mg/dL), respectively. In addition, an unusually high level of insulin auto-antibodies (up to 86%; normal, < 5%) was identified in the patient's serum, and we assumed that these insulin-binding autoantibodies belonged to the IgG class.

To further characterize the endogenous insulin-binding activity of these autoantibodies, we compared sera from a normal subject and from the patient, before and after 50% ammonium sulfate precipitation, with a method described by Redmon et al.[8] Briefly, normal serum, an aliquot of patient's serum, and re-dissolved ammonium sulfate precipitant, were incubated with ^{125}I-labeled insulin for 24 hours at 4°C; the bound fraction was then precipitated with polyethylene glycol. As shown in Table 1, most of the binding activity was retained in the fraction precipitated by ammonium sulfate; this confirmed the presence of insulin-binding Ig in the patient's serum.

The binding characteristics of insulin autoantibodies were further analyzed using an equilibrium-

Table 1. Endogenous insulin-binding activity determined before and after ammonium sulfate precipitation

Serum	Bound insulin (%)	
	Before precipitation	After precipitation
Normal subject	< 3	< 3
Patient	80	49

Serum samples from a control subject and the patient, obtained before and after precipitation with 50% ammonium sulfate, were incubated with ^{125}I-labeled insulin for 24 hours at 4°C. After polyethylene glycol precipitation, the radioactivity of protein-bound ^{125}I-labeled insulin was measured. More than 60% of bound insulin was retained in the precipitate of ammonium sulfate.
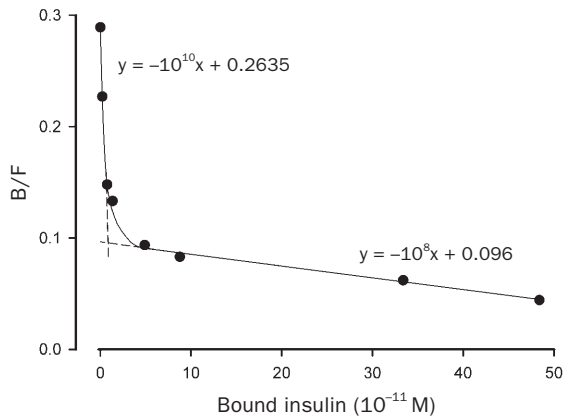
Figure 1. The ratio of bound to free insulin (B/F) for different concentrations of bound insulin (Scatchard plot). Two classes of binding sites were identified: 1 had an affinity constant of 1×10^{10} L/mol and binding capacity of 2.64×10^{-9} mol/L (high affinity/low capacity); the other had an affinity constant of 1×10^{8} L/mol and binding capacity of 9.6×10^{-6} mol/L (low affinity/high capacity).

binding assay described by Goldman et al.[9] First, de-insulinization of the patient's serum was performed by acidification and absorption with dextran-coated charcoal. Then, the serum at a final dilution of 1:5 was incubated for 2 hours at 37°C with ^{125}I-insulin and increasing concentrations of cold insulin. A Scatchard plot of the binding data was then constructed (Figure 1), in which a curvilinear pattern was evident, indicating heterogeneity of the binding sites. Two classes of binding sites were identified: 1 had an affinity constant of 1×10^{10} L/mol and binding capacity of 2.64×10^{-9} mol/L (high affinity/low capacity); the other had an affinity constant of 1×10^{8} L/mol and binding capacity of 9.6×10^{-6} mol/L (low affinity/high capacity), suggesting a polyclonal nature of the autoantibodies.

Capillary blood glucose concentrations were monitored every 2 hours to study the pattern of hypoglycemia in the patient. A 24-hour blood glucose profile revealed post-absorptive hypoglycemia, with a nadir occurring about 3–4 hours after a meal (Figure 2). Both IRI and C-peptide concentrations obtained during hypoglycemia were elevated.

To further define the relationship between the serum concentrations of free insulin, the biologically active fraction of insulin, total insulin, and C-peptide levels, a 5-hour oral glucose tolerance test was performed. After a 100 g glucose load, total insulin level increased markedly at 30 minutes, and declined slowly thereafter, remaining elevated above baseline until 5 hours; free insulin showed only a slight increase. C-peptide level was also raised at 30 minutes, but

began to decline at 2 hours (Figure 3), suggesting a delay in the clearance of insulin.

As isoniazid has previously been associated with hypoglycemia and insulin autoantibodies, it was discontinued. Unfortunately, this patient eventually died from respiratory failure. Permission for autopsy was refused by the family.

Discussion

IAS, first described by Hirata et al in the 1970s, is an extremely rare disorder.[2] To date, approximately 200 cases have been reported, and more than 90% of them were in Japanese patients,[5,6] in whom an underlying autoimmune disease or an exposure history to a sulfhydryl drug, such as methimazole, had been found.[2–6]
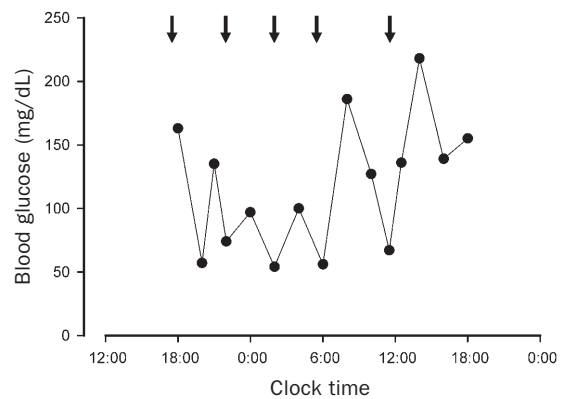
Figure 2. A 24-hour blood glucose profile revealed postprandial hypoglycemia. Black arrows indicate the mealtimes.
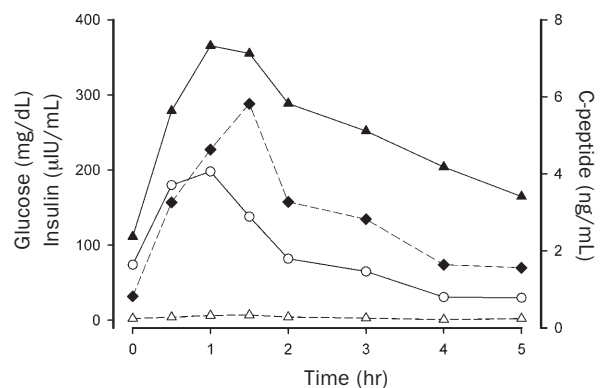
Figure 3. After a 100 g glucose load, total insulin increased markedly, whereas free insulin showed only a slight increase. The level of total insulin remained high until 5 hours, indicating a relatively delayed clearance relative to C-peptide, which began to decline at 3 hours. Glucose (○), free insulin (△), total insulin (▲), C-peptide (◆).

Typically, the hypoglycemic episodes arose during the late postprandial period, and it was assumed that insulin secreted immediately after a meal was bound to autoantibodies and then dissolved from the complex to exert its effect, thus producing postprandial hypoglycemia.[9,10] However, IAS can present with fasting or post-absorptive hypoglycemia. In this situation, it is difficult to differentiate IAS from hyperinsulinemic hypoglycemia due to insulinoma or islet-cell hyperplasia, although IRI level could be a diagnostic clue, since in patients with IAS, the measured insulin level is usually high (sometimes > 1,000 µIU/mL) because of the high capacity of insulin-binding autoantibodies.[2,10–12] However, depending on the insulin antibody used and the method employed for the insulin assay, IRI level may be only mildly or moderately elevated.[5,12] The insulin level (27.22 µIU/mL) of our patient during a hypoglycemic episode was determined by a specific chemiluminescent immunoassay (ADVIA Centaur insulin assay, Bayer Corporation, Tarrytown, NY, USA), which has no cross-reactivity with either proinsulin or C-peptide, rather than by conventional radioimmunoassay; this might explain the low insulin level observed. The method used to determine insulin level (45.7 µIU/mL) during a hypoglycemic episode at the other hospital was unknown.

Redmon et al reported a similar case in which the patient developed postprandial hypoglycemia due to monoclonal insulin-binding antibodies produced by multiple myeloma.[8] In our patient, the markedly elevated levels of total insulin and C-peptide, but much lower level of free insulin, together with the fact that total insulin, unlike C-peptide, 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 autoantibodies. These observations, consistent with the findings of Hirata and Uchigata[6] and Redmon et al,[8] support the notion that the insulin-autoantibody complex is responsible for the development of late postprandial hypoglycemia in patients with IAS.

The binding characteristics of insulin autoantibodies in this case were polyclonal and carried at least 2 classes of binding sites with different affinities and binding capacities, as demonstrated on the Scatchard plot. In agreement with previous observations in most patients with drug-induced IAS,[2,10–12] and in insulin-treated diabetic patients,[9] 1 class of the autoantibody had a high affinity but relatively low binding capacity, whereas the other had a high binding capacity but low affinity. The kinetic characteristics of these insulin-binding autoantibodies, however, were different from those induced by monoclonal gammopathy, in which a single class of binding site alone was found on the Scatchard plot.[8,13]

The cause of IAS is heterogeneous and remains incompletely understood. Underlying autoimmune disorders, specific human leukocyte antigen (HLA) typing, structural abnormalities of insulin, sulfhydryl-containing drugs such as methimazole (most common), thiopronin, penicillamine, glutathione, and other drugs, including hydralazine, procainamide and isoniazid, have been associated with this uncommon syndrome.[2,5,6,12,14,15] Rarely, IAS may result from monoclonal insulin-binding autoantibodies produced by multiple myeloma or benign monoclonal gammopathy.[7,13] Immunogenetic evidence suggests a striking association between polyclonal IAS and specific HLA class II antigens such as DRB1*0406, DQA1*0301 and DQB1*0302.[12] 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.[12] Unfortunately, lack of HLA typing data limited genetic studies in our patient.

Villaume et al reported a woman treated with isoniazid who developed hyperinsulinemic hypoglycemia with a normal C-peptide level.[14] In that article, the authors eliminated the possibility of IAS according to the results of a gel filtration-elution profile, in which the fraction of high molecular weight IRI was not elevated; in addition, insulin-binding antibodies were absent 18 months later. However, insulin-binding antibodies could have been transiently present in the serum.[5] Also, the high total IRI concentration found in the patient is a typical feature of IAS.[2–6] Thus, the possibility of "isoniazid-induced IAS" could not be excluded completely. Furthermore, Trenn et al reported a patient who received anti-tuberculous drugs and developed IAS several years later; however, further discussion was not provided.[15] In the summaries of IAS by Burch et al[5] and Hirata and Uchigata,[6] isoniazid was included as one of the causes of drug-induced IAS. Unfortunately, all the above reports provide neither enough evidence for an association between isoniazid and IAS, nor the possible mechanisms of IAS pathogenesis.

Our patient had taken isoniazid for pulmonary tuberculosis for nearly 1 month before the first hypoglycemic attack. There was no exposure history for insulin or insulin-stimulating drug therapy, and insulinoma/nesidioblastosis were almost completely excluded by imaging and ASVS studies. No underlying autoimmune disorders or other causes of IAS could be traced. Therefore, IAS induced by isoniazid was the

most likely cause of hypoglycemia, but remained unproven due to the short clinical course.

In conclusion, IAS, although uncommon clinically, should be one of the differential diagnoses in patients with hyperinsulinemic hypoglycemia, especially in patients receiving isoniazid therapy.

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