Plasmapheresis-remediable Hyperinsulinemic Hypoglycemia in a Patient with Diabetes, Hypertriglyceridemia, and Cardiomyopathy

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Abstract

We here report a case of plasmapheresis-remediable hyperinsulinemic hypoglycemia without evidence of severe insulin resistance or insulin antibodies. The clinical course and a concise review on hyperinsulinemic hypoglycemia are presented. A 44-year-old man with history of type 2 diabetes, hypertriglyceridemia, and severe dilated cardiomyopathy presented with fasting and postprandial hypoglycemia. Laboratory tests revealed extremely elevated insulin levels (>1000 µIU/mL), non-suppressed C-peptide, and negative insulin antibodies.

Computer tomography (CT) of abdomen and pelvis did not identify any mass in the pancreas. Patient failed conservative medical therapies. As plasmapheresis can remove free and protein-bound insulin, we experimented with plasmapheresis to control the hypoglycemia. After three sessions of plasmapheresis, insulin levels decreased and the patient did not have any hypoglycemic episodes afterwards. We conclude that plasmapheresis can be used to control idiopathic hyperinsulinemic hypoglycemia in patients who failed conservative medical treatments, even if their hyperinsulinemia is not caused by apparent autoimmunity.

Keywords: Hyperinsulinemia; Hypoglycemia; Plasmapheresis

Case Report

A 44-year-old white male experienced recurrent fasting and postprandial hypoglycemia during an admission for decompensated heart failure. He reported hypoglycemia symptoms since his thirties that occurred sporadically and resolved with food ingestion.

The patient had been diagnosed with type 2 diabetes mellitus two years before. His glycemia had been difficult to control; he was briefly treated with metformin and then with insulin glargine and insulin aspart for over a year. Six months before presentation, he switched to U-500 insulin due to the large daily insulin dose of 275 units (divided in 3 preprandial doses).

Table 1: Laboratory findings.

Biochemical Tests	Patient Result	Reference Range
During a spontaneous episode of symptomatic hypoglycemia		
Serum glucose	57 mg/dL	70-115 mg/dL
Insulin	1610 µIU/mL	3-19 µIU/mL
C-peptide	1.28 ng/mL	0.8-3.10 ng/mL
Insulin/C-peptide molar ratio	1609	
Fasting		
Serum glucose	196 mg/dL	70-115 mg/dL
Insulin	474 µIU/mL	3-19 µIU/mL
C-peptide	9.56 ng/mL	0.8-3.10 ng/mL
Other laboratory results		
Insulin antibody	<0.4 U/mL	0.0 – 0.4 U/mL
GAD antibody	<1.0 U/mL	<1.0 U/mL
Hypoglycemia agent screening	Negative	-
TSH	1.47	0.39-4.6 mcg/mL
Rheumatoid factor	<20 IU/mL	<20 IU/mL
ANA	40 titer	<40 titer
dsDNA	<10 titer	<10 titer

In addition, the patient suffered from dilated cardiomyopathy, presumably secondary to viral infection, resulting in systolic heart failure. During this hospitalization, he experienced recurrent fasting and postprandial hypoglycemia with blood glucose levels of 50-60 mg/dL, accompanied by severe adrenergic and neuroglycopenic symptoms. Patient had no access to insulin or insulin secretagogues while in hospital. The urine sulfonylurea screening test was negative. His past medical history was also significant for type IV hypertriglyceridemia, obesity, pulmonary embolism, and seizure. Outpatient medications included U-500 insulin, atorvastatin, fenofibrate, carvedilol, digoxin, lacosamide,

ramipril, spironolactone, and torsemide. Physical examination revealed an obese man without acanthosis nigricans. Laboratory testing revealed hemoglobin A1C of 8.2% and normal liver and renal functions. Cosyntropin stimulation test indicated an adequate cortisol response. The results of the hypoglycemic work-up are summarized in Table 1. Most notably, insulin levels were extremely elevated, while the C-peptide levels were not adequately suppressed during the episodes of hypoglycemia. Computed Tomography (CT) of abdomen and pelvis did not identify any mass in the pancreas or other abdominal organs.

The markedly elevated insulin and non-suppressed C-peptide levels were incompatible with exogenous insulin administration. Due to the magnitude of insulin elevation, and insulin to C-peptide molar ratio >1, an autoimmune form of hypoglycemia was considered. Surprisingly, his insulin antibodies were negative. Patient failed the supplementary diet approach with multiple mixed meals that could provide a sustainable supply of glucose throughout the day. Prednisone 30 mg twice daily was initiated to treat presumed autoimmune form of hypoglycemia. His hypoglycemia improved slightly, but prednisone had to be discontinued after 1 week of use due to fluid retention and worsening heart failure. His comorbidities made him unlikely to be able to tolerate other immunosuppressants. He continued to have severe and frequent hypoglycemic episodes, and his comorbidities required immediate control of hypoglycemia. As plasmapheresis can remove free and potential protein-bound insulin, and deplete potential pathogenic antibodies [1,2], we decided to experiment with plasmapheresis to improve hypoglycemia. The patient underwent three consecutive daily plasmapheresis sessions, each exchanging 1 plasma volume with 5% albumin replacement. His post-plasmapheresis insulin dropped from 1294 to 69 μIU/mL. In the three months after plasmapheresis, he did not have a single episode of hypoglycemia.

Discussion

The differential diagnosis of endogenous hyperinsulinemic hypoglycemia in adults includes insulinoma, β-cell nesidioblastosis, type B insulin resistance, and insulin autoimmune syndrome [3]. The extremely elevated insulin levels and lack of pancreatic mass on imaging in our patient make the first two diagnoses unlikely. Type B insulin resistance is characterized by anti-insulin receptor antibodies [4,5]. These antibodies inhibit binding of insulin to its receptor, stimulate the receptor with insulin-like action, desensitize target tissues to insulin, and down-regulate insulin receptors. Most patients present with severe hyperglycemia, but some develop symptomatic hypoglycemia. The pathogenesis of hypoglycemia in this syndrome appears to be due to the partial agonistic activity of these anti-insulin receptor antibodies.

Most patients with anti-insulin receptor antibodies tend to be middle-aged African American female, invariably have signs of hyperinsulinemia such as acanthosis nigricans, and have other autoimmune diseases such as Hashimoto's thyroiditis. Our patient's absence of autoimmune history, male gender,

and lack of acanthosis nigricans do not favor the diagnosis of type B insulin resistance. Insulin Autoimmune Syndrome (IAS, also called Hirata syndrome) is characterized by fasting hypoglycemia or postprandial hypoglycemia, and high concentration of autoantibodies to native human insulin [6]. The disease is also associated with autoimmunity and shows no predilection to gender. Previous studies have reported that 41% of Asian patients with IAS use medications or health supplements that contain sulfhydryl groups, such as methimazole, penicillamine, captopril, diltiazem, and α-lipoic acid-containing supplements, and some patients have monoclonal gammopathy [7-9].

The sulfhydryl group may interact with the disulfide bonds of the insulin molecule, making them more immunogenic. Since the antibodies have relatively weak affinity for insulin, the antibody-bound insulin readily separates, causing spontaneous hypoglycemia. In addition, antibodies produced against exogenous insulin are sometimes seen in patients undergoing insulin treatment [10]. The binding kinetics of these insulin antibodies is similar to that of those autoantibodies in IAS.

We initially considered the diagnosis of IAS most likely in our patient based on: 1) spontaneous hypoglycemia, 2) significantly elevated insulin level with insulin to C-peptide molar ratio of >1, and 3) exclusion of the 3 other causes of hyperinsulinemic hypoglycemia. However this case is different from classic IAS in a few points, i.e., the absence of insulin antibodies, and the lack of association with other apparent autoimmune diseases, medications with sulfhydryl group, or monoclonal gammopathy. It should be noted that only several autoimmunity markers were measured in this patient and other autoimmune diseases not screened for may be present.

The patient required high dose of insulin prior to the development of hypoglycemia and could possibly have developed insulin antibodies to synthetic insulins that were not detected using current method of quantitative radioimmunoassay. The insulin antibody assay could also be interfered by the high levels of triglyceride in his plasma. Interestingly the hypoglycemia responded dramatically to plasmapheresis. The mechanisms for the plasmapheresis-remediable hypoglycemia are not very clear but plasmapheresis can remove free insulin, any protein-bound insulin, and pathogenic antibodies [1,2]. As there are no measurable insulin antibodies, our patient might alternatively have harbored a protein factor that binds with insulin with high capacity, which is removed by plasmapheresis.

In summary, the cause of this patient's hyperinsulinemic hypoglycemia is not clear but this unique hyperinsulinemic hypoglycemia is refractory to dietary modifications, only slightly responsive to corticosteroid, and is successfully treated by plasmapheresis.

We conclude that plasmapheresis can be used to control idiopathic hyperinsulinemic hypoglycemia in patients who failed conservative medical treatments, even if their hyperinsulinemia is not clearly caused by apparent autoimmunity.

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