Hypoglycemia Due to the Presence of Anti-insulin Antibodies: A Case Report

Anti-insülin Antikorlarının Varlığına Bağlı Hipoglisemi: Bir Olgu Sunumu

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Abstract

A 50-year-old male was referred to our clinic for hypoglycemic attacks. He denied using oral antidiabetic drugs, insulin, or herbal substances but admitted using proton pump inhibitors, pregabalin, and alpha lipoic acid. Venous blood glucose level was 44 mg/dL, C-peptide was 15.6 ng/mL, and insulin levels were >1.000 µIU/mL. His BMI was 21.4. No evidence of pancreatic or extra pancreatic insulinoma was found in imaging studies. No diagnostic results were obtained in the selective calcium receptor stimulation test. Anti-insulin antibody test was positive. The insulin autoimmune syndrome was diagnosed with low glucose levels. The symptoms were associated with very high serum insulin levels, and the patient was positive for the anti-insulin antibody. Alpha lipoic acid and proton pump inhibitors, which may cause insulin autoimmune syndrome, were discontinued and alpha glucosidase inhibitor and diet therapy were started. During follow-up, the patient did not report hypoglycemia. Insulin autoimmune hypoglycemia should be kept in mind in patients with very high levels of insulin and without evidence of insulinoma.

Keywords: Autoimmune; hypoglycemia; anti-insulin antibody

Özet

Elli yaşındaki erkek hasta, hipoglisemik ataklar nedeni ile kliniğimize yönlendirildi. Hasta oral antidiyabetik ilaç, insülin veya bitkisel maddeler kullanmadığını; ancak proton pompa inhibitörü, pregabalin ve alfa lipoik asit kullandığını belirtti. Hastanın venöz kan glukoz seviyesi 44 mg/dL iken, C-peptit düzeyi 15,6 ng/mL ve insülin seviyesi 1.000 µIU/mL üzerinde idi. Beden kitle indeksi 21,4 bulundu. Görüntüleme çalışmalarında, pankreatik veya ekstra pankreatik insülinoma lehine kanıt bulunmadı. Selektif kalsiyum reseptör stimülasyon testinde tanısal sonuç alınamadı. Anti-insülin antikor testi pozitif saptandı. Düşük glukoz seviyeleri ile birlikte insülin otoimmün sendrom tanısı konuldu. Belirtiler çok yüksek serum insülin seviyeleri ile ilişkili idi ve hastada anti-insülin antikoru pozitifti. İnsülin otoimmün sendromuna neden olabilecek alfa lipoik asit ve proton pompa inhibitörleri kesildi ve alfa glukozidaz inhibitörü ile diyet tedavisi başladı. Takip sırasında hasta hipoglisemi tarif etmedi. İnsülin otoimmün hipoglisemi, çok yüksek düzeyde insülin seviyesi ile birlikte insülinoma lehine bulgu olmayan hastalarda akılda tutulmalıdır.

Anahtar kelimeler: Otoimmün; hipoglisemi; anti-insülin antikoru

Introduction

The most common causes of hypoglycemia in non-diabetic patients are insulinoma, extra pancreatic tumors, and autoimmune hypoglycemia (1). The autoimmunity that causes hypoglycemia occurs in two ways: insulin receptor antibodies with insulin mimetic effects or insulin autoimmune syndrome characterized by insulin antibodies (1). The insulin autoimmune syndrome is characterized by spontaneous hypoglycemia, increased insulin levels, and increased

circulating insulin antibodies, first described by Hirata et al. in 1970 (2). It may cause postprandial hypoglycemia but rarely causes fasting hypoglycemia. Despite adequate insulin secretion following ingestion of food or oral glucose loading, hyperglycemia and a hypoglycemic reaction occur after 2-3 h. The reason is that there is less increase in free insulin initially and a slower decrease over time, when compared with total insulin and c peptide. Insulin-antibodies binding insulin that is possibly secreted in response to hyperglycemia reduces the initial insulin response and, consequently, hyperglycemia is exacerbated. This causes further insulin secretion. As the glucose level decreases, insulin secretion and total insulin concentration also decrease. The release of the antibody-bond insulin causes the free insulin to be inappropriately elevated irrespective of the glucose level, and this results in hypoglycemia (3). Insulin autoimmune syndrome has a strong association with sulfhydryl group drug use, some autoimmune diseases, plasma cell dyscrasias, and presence of HLA-DR4. There are also publications showing association with other drugs, which most frequently include methimazole, along with others such as D-penicillamine, procainamide, isoniazid, hydralazine, glutathione, captopril, and imipenem (4). In addition, incidences related to alpha lipoic acid (5) and proton pump inhibitor (1, 2) have also been reported.

Case Report

A 50-year-old man was referred to our clinic on the occasion of fever, sweating and palpitations, which started about a month ago, and a low blood glucose level was detected in another clinic. The patient described the symptoms being aggravated with hunger and 2-3 h after the meal. He had food cravings 2 or 3 times a night.

However, the patient stated that he had fasted in Ramadan about five months ago and the duration of the fasting period reached 17 h and his complaints were absent at that time.

The patient denied any chronic disease; however, pregabalin was prescribed in a clinic due to chills and tingling in the feet and the hands. During this period, he admitted intermediate usage of proton pump inhibitors (esomeprazole and rabeprazole) and vitamin complexes including B1 +B6 + B12 + alpha lipoic acid.

On physical examination, his general condition was good, body temperature was 36.6 degrees, pulse rate was 80/min, blood pressure was 110/70 mmHg. The patient's body mass index was calculated as 21.4, with a height of 174 cm and a weight of 65 kg. No pathology was detected in the systemic examination. At the time of admission, the blood glucose level was 54 mg/dL. Renal function, liver function, thyroid function tests, and complete blood count values were normal. The patient was negative for thyroid auto antigens, ANA, and RF values; the HbA1c value was 5.74.

He was hospitalized and followed up for the signs of hypoglycemia. The tests which were performed during a hypoglycemic period did not show pathology with counter insulin system function to show endogenous hyperinsulinemia.

The blood glucose level was 44 mg/dL, insulin level >1000 µl/mL, c peptide 15.6 ng/mL, growth hormone 16.49 ng/mL, and cortisol response was 26.41 *µg/dL*. These tests were performed using a Cobas 8000 Autoanalyzer (Roche Diagnostics, Mannheim, Germany) and the enzymatic colorimetric method. ACTH level was 66.4 pg/mL. The ACTH test was performed using the electrochemiluminescence immunoassay (ECLIA) method in a Roche Hitachi Cobas e411 Analyzer (Roche Diagnostics, Mannheim, Germany).

The prolactin and parathormone levels were in the normal limits ruling out MEN. Ultrasound of the pancreas with a preliminary diagnosis of insulinoma showed normal homogeneous appearance and pathology was not detected in other organs. No pathology was detected in dynamic pancreas computerized tomography. Abdomen/pelvis MRI and Ga-68 DOTATATE PET/CT examinations were normal and an extra pancreatic focus was ruled out. In order to rule out insulinoma, selective calcium receptor stimulation test was performed. During the test, 0.015 mEq/kg of calcium was delivered via the catheterized arteries (hepatic artery, splenic artery, gastroduodenal artery, and superior mesenteric artery). A blood sample of 5 mL was taken from the hepatic vein, before calcium injection and at 30 s and at 1, 1.5, 2,

3 min. At least a two-fold increase in insulin levels in blood samples taken at 30 s and first minute after calcium injection suggests the presence of an insulin secreting tumor in the artery-fed region (6). In our patient, insulin levels were >1000 units in all samples. The results obtained when the serum samples were diluted and reworked are shown in Table 1. The results obtained were not conclusive in terms of localizing the presence of an insulin secreting tumor.

The baseline blood glucose level was 57 mg/dL and the insulin level was 2939 units in the 75 g OGTT test. At the first hour, the blood glucose level was 201 mg/dL, insulin level was 4038 *u/mL*, blood glucose level was 39 mg/dL, and insulin level was 4655 *u/mL* at the 4th hour when the lowest blood sugar of the patient was reached.

The insulin autoantibody test was positive. The patient was diagnosed with insulin autoimmune syndrome. The dietary arrangement was made available at the hospital and acarbose treatment was started. Hypoglycemia complaints did not recur in the follow-up under current treatment.

Discussion

Endogenous hyper insulinemia hypoglycemia (EHH) is a condition resulting in the excessive low levels of glucose due to endogenous excess insulin production. The most common cause of EHH is insulinoma, though insulin autoimmune syndrome should also be taken into account as a rare cause of EHH (4).

This study presents a case of insulin autoimmune syndrome resulting in high serum insulin levels, while the positivity of insulin autoantibodies during hypoglycemia and imaging methods were completely normal in terms of insulinoma.

Earlier studies have shown much higher levels of insulin in insulin auto immune syndrome in contrast to insulinoma. Woo CY and colleagues analyzed 84 patients with EHH during 1998-2012 and observed that the patients with insulinoma had a mean insulin level of 14.1 mIU/mL; however, it was over 1000 mlU/mL in insulin autoantibody positive patients (7). This elevation in insulin levels is explained by the delay in clearance of insulin in the absence of auto antibodies which bind insulin (8). In our patient Insulin levels were also >1000 mlU/mL as expected. Our patient did not show symptoms despite the fact that he was fasting for a long time during the month of Ramadan (three months before the admission) and he had hypoglycemic symptoms at 4th hour in OGTT. This also supports the diagnosis of insulin autoimmune hypoglycemia. In a case report by Pooja and colleagues, neuroglycopenic symptoms in a patient with insulin autoimmune hypoglycemia were observed after 2 h of a meal (2).

The drugs containing sulfhydryl groups are known to be associated with insulin autoimmune hypoglycemia (2, 6). In addition, case reports showing association with alpha lipoic acid (5) and with proton pump inhibitors containing sulfhydryl groups (2) have been reported. The mechanism of how sulfhydryl group containing drugs develop insulin autoimmune hypoglycemia is unclear (2). Gopal et al. reported a case report of insulin autoimmune hypoglycemia due to pantoprazole use. When pantoprazole is activated in the acidic medium, sulfonic acid is formed and is attached to the sulfhydryl group of H^+ K^+ ATPase. This is related to the fact that the active form of the drug binds to the disulfide bond in the insulin molecule and makes the

	GDA	SMA	HA	SA right	SA left
0. sec	4224	5669	3922	3614	5173
30. sec	6218	4339	5900	3981	3524
1. min	6325	6263	6833	6295	5808
1,5 min	6369	6272	5903	6216	5860
2. min	6418	7687	6340	5599	6060
3. min	6540	6160	6490	4001	5883

Table 1. The results of selective calcium receptor stimulation test.

GDA: Gastroduodenal artery; SMA: Superior mesenteric artery; HA: Hepatic artery; SA: Splenic artery.

insulin immunogenic (1). In a case report published by Pooja et al., omeprazole use was associated with insulin autoimmune hypoglycemia (2). Our patient also had a history of vitamin complex containing alpha lipoic acid and esomeprazole usage in the last three months. Insulin autoantibody positivity that we detected in our patient may be associated with the use of these drugs. Insulin autoimmune hypoglycemia is usually a self-limiting disease. Many patients respond to a high frequency diet well. Alpha glycosidase inhibitors reduce postprandial insulin levels and thus reduce postprandial hypoglycemic episodes. Steroid, diazoxide, octreotide and plasmapheresis treatments can be tried in patients who do not respond to these treatments (1).

In our patient, hypoglycemia did not occur under dietary management and acarbose therapy.

In conclusion, in patients with hypoglycemia showing very high levels of insulin and no other diagnosis could be made with imaging modalities, insulin autoimmune syndrome should be considered for further differential diagnosis as a rare cause of EHH.

Source of Finance

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Belgin Efe; Design: Belgin Efe, Elif Sevil Alagüney; Control/Supervision: Belgin Efe, Elif Sevil Alagüney; Data Collection and/or Processing: Belgin Efe, Elif Sevil Alagüney, İnsaf Durmuş; Analysis and/or Interpretation: Belgin Efe, Göknur Yorulmaz, Elif Sevil Alagüney; Literature Review: Belgin Efe, Elif Sevil Alagüney; Writing the Article: Elif Selvi Alagüney; Critical Review: Belgin Efe.

References

1. Gopal K, Priya G, Gupta N, Praveen EP, Khadgawat R. A case of autoimmune hypoglycemia outside Japan: Rare, but in the era of expanding drug-list, important to suspect. Indian J Endocrinol Metab. 2013;17:1117-1119. [Crossref] [PubMed] [PMC]

2. Sahni P, Trivedi N, Omer A. Insulin autoimmune syndrome: a rare cause of postprandial hypoglycemia. Endocrinol Diabetes Metab Case Rep. 2016;1-4. [Crossref]

3. Türkiye Endokrinoloji ve Metabolizma Dernegi (TEMD). Baskal N. Hipoglisemi. Klinik Endokrinoloji. Ankara: Miki Matbaacılık San ve Tic Ltd Şti; 2000:69-75.

4. Alam S, Ozair M, Ahmad J. Hypoglycemia due to insulin autoimmune syndrome: a rare cause not to be forgotten. Journal of Clinical and Translational Endocrinology: Case Reports. 2016:7-9.

5. Gullo D, Evans JL, Sortino G, Goldfine ID, Vigneri R. Insulin autoimmune syndrome (Hirata Disease) in European Caucasians taking alpha-lipoic acid. Clin Endocrinol (Oxf). 2014;81:204-209. [Crossref] [PubMed]

6. Pereira PL, Roche AJ, Maier GW, Huppert PE, Dammann F, Farnsworth CT, Duda S, Claussen CD. Insulinoma and islet cell hyperplasia: value of the calcium intraarterial stimulation test when findings of other preoperative studies are negative. Radiology. 1998;206:703-709. [Crossref] [PubMed]

7. Woo CY, Jeong JY, Jang JE, Leem J, Jung CH, Koh EH, Lee WJ, Kim MS, Park JY, Lee JB, Lee KU. Clinical features and causes of endogenous hyperinsulinemic hypoglycemia in Korea. Diabetes Metab J. 2015;39:126-131. [Crossref] [PubMed] [PMC]

8. Ma WY, Won JG, Tang KT, Lin HD. Severe hypoglycemic coma due to insulin autoimmune syndrome. J Chin Med Assoc. 2005;68:82-86. [Crossref]