Turkish Journal of Internal Medicine
http://www.tjim.org
ISSN: 2687-4245
Case Report

An Unusual Cause of Hypoglycemia: Insulin Autoimmune Syndrome

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Abstract

Insulin autoimmune syndrome (IAS) is a rare cause of hyperinsulinemic hypoglycemia characterized by antibodies to endogenous insulin without exposure to exogenous insulin. In this report, we presented a case of insulin autoimmune syndrome with a history of fasting hypoglycemia. After work up and exclusion of other causes such as insulinoma, hyperinsulinemic hypoglycemic state of the patient was considered to have been induced by etofenamate. Although IAS is generally self-limiting and dietary management and withdrawal of trigger drug are enough to maintain euglycemia, in some cases corticosteroids, plasmapheresis, rituximab can be used for treatment. In our case, despite dietary management, hypoglycemia was severe and the patient's life quality was adversely affected. After treatment with prednisolone, hypoglycemic episodes became less and less frequent. IAS should be considered as a differential diagnosis of hyperinsulinemic hypoglycemic states to avoid unnecessary interventions.

Turk J Int Med 2021;3(1):32-36
DOI: 10.46310/tjim.786828

Keywords: *insulin autoimmune syndrome, hyperinsulinemic hypoglycemic state, corticosteroids*

Introduction

Insulin autoimmune syndrome (IAS) is characterized by hypoglycemia and presence of antibodies to endogenous insulin in insulin naive patients. This syndrome is also known as Hirata's disease who first described the syndrome in 1970.[1]

Viruses and mostly drugs trigger formation of anti-insulin antibodies. Autoantibodies bind to insulin molecules secreted from pancreas following meal and rendering them unable to exert their effects. As glucose concentration falls, insulin molecules dissociate from the autoantibodies and causes hypoglycemia.[2]

Received: October 5, 2020; Accepted: December 18, 2020; Published Online: January 29, 2021

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In IAS, insulin and C-peptide levels are high and antibodies to insulin are positive. The patients are not having a history of exposure to exogenous insulin. Several autoimmune diseases can be associated with this syndrome. The first line treatment is withdrawal of trigger drug and diet with low glycemic index but in some severe cases other treatment strategies can be considered like prednisolone.

Case Report

A 55-year-old male patient with a history of hypertension and chronic obstructive pulmonary disease was presented to endocrinology clinic with a month history of symptoms of hypoglycemia such as weakness and sweating. Hypoglycemia attacks were occurred in the fasting period and alleviated with food intake. Detailed history review did not identify any suspicion for insulin and/or insulin secretagogues, herbal substances. He did not smoke or drink alcohol. There was no known diagnosis of diabetes mellitus in the patient and his family history. His symptoms of hypoglycemia had started after using etofenamate, nonsteroidal anti-inflammatory medication, administered intramuscularly due to lower back pain for a month. Vital signs were normal and physical examination was not significant.

In laboratory evaluation, complete blood count, renal, liver and thyroid function tests were normal. ACTH - cortisol axis was evaluated as normal. A random blood glucose level was 146 mg/dL. During the follow up, fingerstick blood glucose levels were observed as in Table 1.

When the patient's fingerstick blood glucose level was 44 mg/dL, he was symptomatic and experienced sweating and weakness. Blood samples were collected during hypoglycemic attack and then he was given continuous intravenous infusion of dextrose to sustain euglycemia. Laboratory investigations taken during hypoglycemia indicated that hypoglycemia was associated with markedly increased insulin and C-peptide levels compatible with hyperinsulinemic hypoglycemic state *(Table 2)*.

There was no pathological finding in the abdominal computed tomography evaluated for insulinoma. Selective arterial calcium stimulation test was performed to differentiate pancreatic pathologies.

Regardless of the sampling site, all specimens taken from different site had raised insulin and C-peptide levels *(Table 3)*. As insulin to C-peptide molar ratio >1 and autoantibodies to insulin were found to be markedly increased at more than 100 IU/mL (reference range: 0-10 IU/mL), autoimmune hypoglycemia was considered as the cause of hypoglycemia.

Etiology of autoimmune hypoglycemia was considered due to usage of etofenamate; so that it was discontinued. The patient was advised to start a low glycemic index diet with frequent small meals. The diet was insufficient to improve the hypoglycemic attacks so that prednisolone treatment was started as 30 mg daily. Work up for other autoimmune diseases revealed increased anti-double stranded DNA (anti-dsDNA) level of 38 IU/mL (12-18) and positive anti-nuclear antibody (ANA) level, elevated anti thyroid

Table 1. Fingerstick blood glucose levels

	Morning blood glucose (mg/dL)		Noon blood glucose (mg/dL)		Evening blood glucose (mg/dL)		Overnight blood glucose (mg/dL)
	Fasting	Postprandial	Fasting	Postprandial	Fasting	Postprandial	
First day					156	172	52 - 96
Second day	56	87	108	214	166	103	69 - 157
Third day	41	59	78	205	55	116	70

Table 2. Laboratory investigations performed during hypoglycemic period

Parameters	Results	Reference ranges
Serum glucose (mg/dL)	44	70 - 100
Serum insulin (mIU/L)	>600	2.6 – 24.9
Serum C-peptide (µg/L)	7	0.78 – 5.19
Insulin/C-peptide molar ratio	>85.7	<1

peroxidase antibody (anti-TPO) level of 34.8 KU/L (0-5.61), elevated anti thyroglobulin antibody level of 20 KU/L (0-4.11). Imaging studies for thyroid gland was compatible with autoimmune thyroid disease. After consultation to rheumatology clinic, no pathology was considered. Also, blood work for monoclonal gammopathy was not significant.

During hospital stay, the occurrence of hypoglycemic episodes decreased, and he was stopped intravenous dextrose infusion. Since he remained euglycemic with treatment of prednisolone, dosage of treatment was gradually decreased to 20 mg/day.

At his follow up visit, two months after discharge from hospital, hypoglycemia did not occur and his dosage of prednisolone treatment was decreased to 15 mg/day. His most recent laboratory investigations demonstrated persistently raised anti insulin antibody levels >100 IU/mL (reference range: 0-10 IU/ mL). In the follow up of the patient, it was planned that the prednisolone treatment should be gradually decreased and discontinued.

Discussion

IAS is a rare cause of hyperinsulinemic hypoglycemia. This syndrome is characterized by autoantibodies to endogenous insulin without pathology of pancreatic islet cells in patients without history of previous exposure to exogenous insulin.[3] It is usually seen in adults older than 40 years of age. At least 400 cases have been seen in Japan[4] and it is more common in Asian people.

The etiology of antibody formation is multifactorial. Exposure to drugs, viral infections like mumps, rubella, influenza, measles, autoimmune diseases like Graves' disease, hematologic diseases like multiple myeloma can trigger autoimmune hypoglycemia syndrome.[5-7] Also, strong association was observed with the presence of human leukocyte antigen (HLA-DR4) in cases.[8] IAS is associated with exposure to medications containing a sulfhydryl group like methimazole, captopril, hydralazine, procainamide etc.[9] In the literature, patients developed IAS response to nonsteroidal antiinflammatory drugs such as loxoprofen

Table 3. Selective arterial calcium stimulation test results

Time (seconds)	Insulin levels (mIU/L)		
	Superior mesenteric artery	Gastroduodenal artery	Splenic artery
0. sec	2082.6	2028.9	2088.6
20. sec	2026.3	2162.8	2121.5
40. sec	2021.4	2116.8	2064.6
60. sec	2098.6	2117.5	2109.4

sodium and diclofenac sodium. In our case unlike the literature, onset of hypoglycemia after intake of etofenamate treatment of lower back pain suggested IAS.[3]

After food intake, autoantibodies bind to secreted insulin and proinsulin making the insulin to be ineffective. This causes postprandial hyperglycemia and increasing insulin release from pancreas. After dissociation insulin from antibodies, high levels of insulin cause hypoglycemia.[5]

Hypoglycemia can be observed on fasting state or postprandially in IAS. In our case fasting hypoglycemia was observed. The patient experienced hypoglycemia symptoms especially in the overnight period and before breakfast in the morning. Due to insulinoma is the first preliminary diagnosis that comes to mind, with the combination of fasting hypoglycemia and endogenous hyperinsulinemia, the investigations planned in this direction. Because of no mass in pancreas in the abdominal computed tomography, very high levels of insulin and C-peptide, excessively high values at insulin levels in all samples in the calcium stimulation test and positivity of anti-insulin antibody, autoimmune hypoglycemia was considered as diagnosis in our case. Positivity of ANA and elevated thyroid autoantibodies supported the association of IAS and autoimmunity.

In IAS, antibody bounds to insulin, half-life of insulin increases from 5 minutes to hours, while the half-life of C-peptide usually remains unaffected (30–35 minutes).[10] Patient with IAS thus have more than one insulin to C-peptide molar ratio.

IAS is generally self-limiting, and most patients can achieve remission of the disease after stopping use of the medication.[11] Food with low glycemic index remains the first line of the treatment to avoid postprandial hyperglycemia and then secretion of insulin. In more severe cases like in our case, euglycemia can be achieved by using corticosteroid therapy.

As we did not consider interference from heterophile antibodies, we did not do heterophile antibody test. Treatment with prednisolone and then clinical improvement of the patient may suggest that interference was low.

Consequently, for diagnosis, patient's detailed history including age, sex, personel and family history of diseases such as autoimmune and hematological diseases, intake of any drugs or health supplements, infections, time and mode of hypoglycemia is very important. In all hyperinsulinemic hypoglycemic cases, especially in patients taking medications known to be associated with this syndrome and having very high insulin levels, the diagnosis of IAS should be kept in mind.

Conclusion

IAS should be considered as a differential diagnosis in hyperinsulinemic hypoglycemic patient to avoid any unnecessary and invasive procedures.

Conflict of Interests

Authors declare that there are none.

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