Case report

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A 43-year-old man with recurrent spontaneous hypoglycemia

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Abstract

Insulin autoimmune syndrome (IAS) is a rare hypoglycemic disorder characterized by recurrent episodes of fasting or late post-prandial hypoglycemia with a very high level of insulin and positive insulin antibody. We are reporting a case of recurrent episodes of spontaneous hypoglycemia in a 43-year-old male with biopsy-proven autoimmune hepatitis. After a thorough evaluation, he was found to have endogenous hyperinsulinemia. As there was no apparent cause of endogenous hyperinsulinemia, he was evaluated for insulin antibody which was found to be raised. A diagnosis of IAS was made, and he was put on a small frequent meal with tab diazoxide, and he improved. Although it is an uncommon disease, it should be kept in the differential diagnosis of spontaneous hypoglycemia. *[J Assoc Clin Endocrinol Diabetol Bangladesh,* July 2024;3(2)*: 71-74]*

Keywords: Insulin autoimmune syndrome, hypoglycemia, insulin antibody

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Introduction

Insulin autoimmune syndrome (IAS) is a rare cause of hypoglycemia in a person without diabetes. Also known as Hirata's disease, IAS is characterized by episodes of spontaneous hypoglycemia, high insulin, and positive insulin autoantibodies in individuals not getting exogenous insulin.[1] It is primarily reported to occur among persons of Japanese or Korean ethnicity. The first case was reported by Hirata et al. in 1970, and it is the third most common cause of hypoglycemia in Japan.[2]

Insulin autoimmune syndrome has an association with other autoimmune diseases or exposure to the sulphydryl group of drugs. Symptoms usually occur in a late post-absorptive state but may also occur in a fasting state or both.[3] Although the pathogenesis that underlies the disease is not clear, insulin secreted in response to meal is thought to bind to antibodies and dissociate in an unregulated fashion, resulting in hyperinsulinemia and hypoglycemia.[4] Clues to the diagnosis are very high levels of insulin at the time of hypoglycemia and high titer of insulin autoantibody.[5] Most patients with IAS require no treatment and have spontaneous remission within 3-6 months.[6]

Very few cases have been reported worldwide. The incidence of IAS in Bangladesh is Not exactly known. It is important to keep this differential diagnosis in patients with hyperinsulinemic hypoglycemia. We report a very interesting case of a 43-year-old man who presented with hyperinsulinemic hypoglycemia and autoimmune hepatitis. He had a positive high titer of insulin antibodies, leading to the diagnosis of IAS.

Case report

A 43-year-old man complained of recurrent episodes of hypoglycemia, which occurred initially 3-4 hours after a meal but later also occured in a fasting state. He had symptoms of palpitation, sweating, and blurring of vision, which improved after taking sugary drinks. Self-measured capillary blood glucose values were found to be low during those episodes, thus fulfilling Whipple's triad. Symptoms began about 2 months back. In the initial part, symptoms used to occur every 2-3

days apart, but for the last few days, symptoms tend to occur almost every day. He had been diagnosed with autoimmune hepatitis 4 months back based on histopathology of liver biopsy. He received oral Prednisolone 40 mg daily for 3 months, and he was getting oral Azathioprine 50 mg daily for autoimmune hepatitis when he presented to us with hypoglycemic symptoms. He was also diagnosed with hypertension, for which he was on Losartan 50 mg daily. He had no previous history of diabetes mellitus, endocrinopathies, or use of exogenous insulin or sulphonylurea. His physical examination was unremarkable, with no acanthosis nigricans. His body mass index (BMI) was 23.47 Kg/m^2. His lowest capillary blood glucose was 2 mmol/l, measured during the period of hypoglycemic symptoms. Laboratory investigations are listed in Table-I. Both insulin and C-peptide levels were markedly elevated at the time of hypoglycemia. A contrast CT scan of the whole abdomen was negative for any pancreatic mass. Insulin antibody titer was markedly elevated >175 IU/ml (normal value <20 IU/ml) measured by Chemiluminescence immunoassay, and insulin level was persistently elevated (>300 microIU/ml).

The patient was advised to take a small frequent meal by following the hypoglycemia meal chart at 3-4 hour intervals and maintaining a self-monitored blood glucose chart. His hypoglycemic episodes were reduced to a significant state with frequent feeding. Oral Diazoxide 25 mg was started, which was titrated to 100 mg daily. The patient complained of no further hypoglycemic episodes to date, and their fasting insulin level decreased significantly without any side effects of diazoxide. Self-monitored blood glucose levels and fasting insulin before and after dietary adjustment and treatment with diazoxide are shown in Figure 1 and Figure 2 respectively.

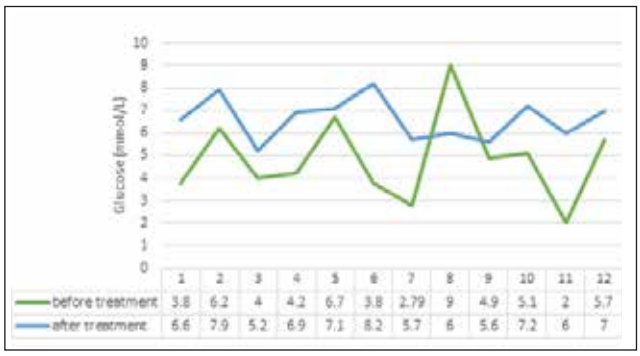

Figure-1: Capillary blood glucose before and after treatment

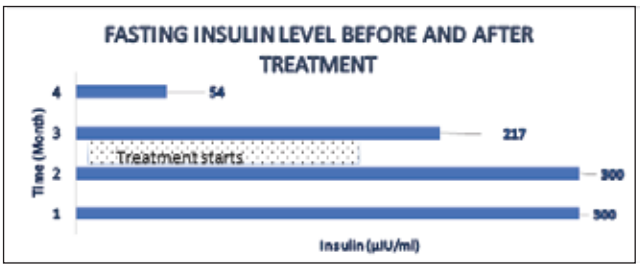

Figure-2: Fasting insulin level before and after treatment

Discussion

IAS, or Hirata disease, is an uncommon cause of hypoglycemia. IAS is the third most common cause of hypoglycemia in the Asian population, following insulinoma and extrapancreatic malignancy. It affects the male and female sex indiscriminately and is more common among people aged > 40 years.7 Our patient was a 43-year-old male which is consistent with the

Table-I: Laboratory investigations

Variables	Results	Normal values
Plasma glucose at the time of hypoglycemia (mmol/L)	2.4	3.5-6
Insulin level during hypoglycemia (micro IU/ml)	>300	2.6-37.6
C-peptide during hypoglycemia (ng/ml)	5.39	1.1-4.5
HbA1c	5%	4.5-6.3%
Insulin autoantibody (IU/ml)	>175	<20
SGPT (U/L)	72	10-49
Serum creatinine (mg/dl)	0.83	0.7-1.3
Serum Cortisol (nmol/l)	431.80	138-690
Plasma ACTH (pg/ml)	78.8	0-46
CT scan of whole abdomen	Mild hepatic steatosis, mild splenomegaly	-
Insulin level after 2 months of treatment (micro IU/ml)	217	-
Insulin level after 4 months of treatment (micro IU/ml)	54	-

average age group.

IAS has a frequent association with other autoimmune diseases like Graves' disease, rheumatoid arthritis, SLE, and the use of medications containing the sulphydryl group.[8] Among drugs, methimazole, captopril, D-penicillamine, imipenem, clopidogrel, hydralazine, diltiazem, etc, have been reported to cause IAS.[7] Our patient had no history of exposure to these medications, but he had been diagnosed with autoimmune hepatitis.

The exact pathogenesis behind IAS is not completely understood. Hypoglycemia is hypothesized to result from a mismatch between free insulin concentration and blood glucose level.[7] After meals, insulin antibody binds with insulin secreted by increased glucose load. The insulin antibody complex hinders the physiological action of insulin. Parallel to decreased blood glucose level, the insulin that is bound to antibodies is released, leading to a mismatch between free insulin concentration and blood glucose level, causing late post-prandial hypoglycemia.[3] IAS thus classically causes late post-prandial hypoglycemia but may cause fasting hypoglycemia.[8] Consistent with this kinetics of the insulin antibody complex, we can infer that our patient had hypoglycemic episodes in the late post-absorptive and fasting states.

In patients with significant hypoglycemia, diagnostic workup must include insulin concentration along with c-peptide to rule out insulinoma and exogenous insulin use.[8] An extremely high level of insulin (>300 microIU/ml) in our patient favors the diagnosis of IAS as the insulin level seldom exceeds 100 microIU/ml in the case of insulinoma. High levels of insulin can be explained by delayed clearance of insulin as it binds to antibodies.[9] In patients with insulinoma, the molar ratio of insulin to c-peptide is <1, whereas in the case of IAS and exogenous insulin, the molar ratio is usually >1.8 Insulin half-life increases from 5 minutes to hours when insulin binds to antibodies, whereas the half-life of c-peptide remain unchanged in case of IAS.[7] Thus, molar ratio of insulin to c-peptide more than 1 points toward the presence of insulin autoantibodies in appropriate clinical context.[8] In our patient, the insulin to c-peptide ratio was 1.2. The presence of a high titer of insulin antibody (>175 microIU/ml) confirms the diagnosis of IAS in our patient. The possibilities of Insulinoma and extrapancreatic malignancy were also excluded by abdominal contrast-enhanced CT scan.

Currently, there is no consensus on the first-line therapy of IAS. Most of the patients have had spontaneous remission without treatment.[8] In the case of drug-induced IAS, discontinuation of the offending drug causes remission within the next few months.[3] It is recommended that patients with IAS should have small but multiple meals and avoid high sugar and carbohydrate-containing food.[8] Despite the spontaneous resolution of symptoms, most patients were treated with different regimens by different investigators. Management of IAS, as reported by various case reports, includes different immunosuppressive regimens such as prednisolone, hydrocortisone, azathioprine, rituximab, cyclophosphamide, mycophenolate mofetil and plasmapheresis and also strategies aiming at reducing insulin levels such as diazoxide, octreotide or even pancreatectomy.[7,10] Our patient was advised to take small frequent meals and monitor capillary blood glucose strictly. His hypoglycemic episodes were reduced significantly with dietary modification. As his symptoms of hypoglycemia started while on prednisolone 30 mg daily and azathioprine 50 mg daily for autoimmune hepatitis, we started tab diazoxide 25 mg daily, stopping prednisolone after consultation with a hepatologist. Azathioprine was continued for autoimmune hepatitis. The dose of diazoxide was increased up to 100 mg daily without any side effects. The patient did not experience any hypoglycemic event till now. Insulin antibodies decline gradually in many cases, but the patients should be regularly followed.[9] Our patient is on regular follow-up and is currently asymptomatic.

Conclusion

The diagnosis of IAS is challenging, requiring careful workup for the exclusion of other causes of hypoglycemia. Failure to localize an abdominal tumor and a high level of insulin raises the suspicion of IAS. The gold standard diagnostic tool is the measurement of insulin antibody. Clinical awareness and high index suspicion of IAS can lead to the avoidance of unnecessary invasive procedures and surgical interventions.

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Disclosure

The authors have no multiplicity of interest to disclose.

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Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethical Approval and Consent to Participate

Written informed consent was obtained from the patient. All methods

were performed in accordance with the relevant guidelines and regulations.

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