Case Report

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Insulin Autoimmune Syndrome: A Rare Etiology of Hypoglycemia: Case Report

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Abstract

Background: A rare form of hypoglycemia called insulin autoimmune syndrome (IAS) occurs when someone who has never been exposed to endogenous insulin develops insulin auto antibodies. As far as our knowledge goes, only 30 cases have been reported in India. Here we report one case of insulin autoimmune syndrome diagnosed and managed in our hospital.

Case Presentation: We present a case of a 68 year-old male who presented with recurrent episodes of post-prandial hypoglycemia. On biochemical evaluation, he was found to have hyper insulinaemic hypoglycemia. Localization studies with CT abdomen were negative for insulinoma. The diagnosis was confirmed by elevated blood levels of insulin auto antibodies. The patient was treated with frequent low carbohydrate meals and high dose corticosteroids. The patient's condition improved, and able to maintain euglycemia on a low dose of corticosteroids.

Conclusion: IAS is a rare endogenous cause of hyper insulinaemic hypoglycemia. It should be suspected in patients presenting with post prandial hypoglycemia, with high insulin and C peptide levels.

Keywords: Insulin Autoimmune syndrome; Post prandial Hypoglycemia; Insulin auto antibodies; Low carbohydrate meal.

INTRODUCTION

Insulin Autoimmune Syndrome (IAS), also known as Hirata's disease, is a rare cause of hypoglycemia and is characterized by episodes of spontaneous hypoglycemia and insulin auto antibodies in individuals who have not received exogenous insulin.[1] It is Japan's third most common cause of hypoglycemia after insulinoma and extra pancreatic neoplasias, with more than 300 cases of this syndrome reported.[1] On the other hand, in India, only 30 cases of IAS have been reported to the best of our knowledge.[2] This study presents a successfully treated and diagnosed case of IAS.

CASE REPORT

A 68-year-old man was brought to the emergency

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room for unconsciousness and undetectable blood sugar. He had no history of diabestes , hypertension, alcoholism or oral hypoglycemic agents.

The patient complained of of unconsciousness and 4-5 episodes of hypoglycemia. His symptoms started one month back when he used to have uneasiness and mild sweating after a few hours of food intake, which was relieved after consuming sugar. One day, he had one episode of unconsciousness; he was brought to our hospital, where his random plasma glucose was found to be 30 mg/dl, and he regained consciousness after the administration of an intravenous 25% dextrose infusion. He was transferred to the endocrine unit for further evaluation. His past medical history was significant for arthritis and chronic kidney disease. He had been taking NSAIDs for five years.

There were no significant findings on physical examination. His serum c-peptide level was 25.8 ng/ml (normal range: 1.1 -4.4 ng/ml) and his serum level was 392.7 7 µU/mL (normal range 2.6-24.9µU/mL). The insulin to C-peptide molar ratio was 0.33 (less than 1). The laboratory values raised suspicion about endogenous insulin production. Other laboratory tests were with in normal limits. Exception of high creatnine level of 2.23 and low morning serum cortisol 24 nmo l/l (normal 82.8-579.6 nmol/l) were found. No abnormalities in the pancreas were detected during an abdominal MRI of the patient. Due to Chronic kidney disease, Contrast Enhanced CT Scan of the Upper abdomen (triple phase) could not be done. To confirm the diagnosis, insulin antibody titers were measured by enzyme immunoassay; the level was 34.77 U/mL (normal range <12 U/mL). Other autoantibodies tested did not produce positive results , except for weakly positive rheumatoid factors titres (13.4).

Table 1: Laboratory Tests

Laboratory test	Results	Reference Range
Hemoglobin (g/dL)	15.3	12.5-16.3
White blood cells (×103/µL)	6.22	3.6-10.2
Platelets (x103/µL)	243	152- 348
Glucose (mg/dL)	55	74-106
HbA1c (%)	5.2	<6.2
Creatinine (mg/dL)	2.23	0.67-1.17
Alanine Transaminase (U/L)	16	<33
Albumin (g/dL)	3.7	3.5-5.1
Potassium (mmol/L)	4.2	3.5-5.2
Sodium (mmol/L)	133	136-145
Thyroid stimulating hormone (mIU/L)	2.2	0.4-4.5
Insulin (µIU/mL)	392.7	2.6-24.9
C-peptide (ng/mL)	25.8	1.1-4.4
Serumketone (mmol/L)	0.2	0.02-0.2
Cortisol 8 am (nmol)	24	82.8-579.6
Anti-Insulin (U/mL)	34.77	<10
HBsAg	Negative	–
AntiHCV	Negative	–
HIV Antibody	Negative	–
Antinuclear Antibody	Negative	–
P-Anti-neutrophil Cytoplasmic Antibody	Negative	–
Anti Double-stranded DNA Antibody	Negative	–
Rheumatoid Factor (IU/L)	13.4	<14
Anti TPO Antibody (IU/ml)	<30	0-34
Glucose (mg/dl)	45	74-106
Serum Insulin (uIU/L)	794	2.6-24.9
C-Peptide (ng/ml)	37.1	1.1-4.4

During admission, he never developed fasting hypoglycemia; it was observed in the post absorptive phase. At that time, his blood sugars dropped to 45 mg/dl, accompanied by an insulin level of 794uU/ml and C-peptide 37.1 ng/ml. Insulin Autoimmune Syndrome was diagnosed despite the insulin to C-peptide molar ratio being <1, due to the presence of high insulin antibody titers, post prandial hypoglycemia, and the absence of any pancreatic lesion.

The patient was placed on frequent low carbohydrate meals, and oral hydrocortisone was started (40mg/day), but he continued to develop hypoglycemic episodes with higher doses (120mg/day). So we switched to oral prednisolone with a starting dose of 60 mg/day and increased to 100mg/day until his blood sugar stabilized. After one month of treatment with 30mg/day of hydrocortisone, his blood sugar levels were maintained. Six months later, the dosage was reduced to 15mg/day and his

blood sugar levels remained stable (Fig. 1).

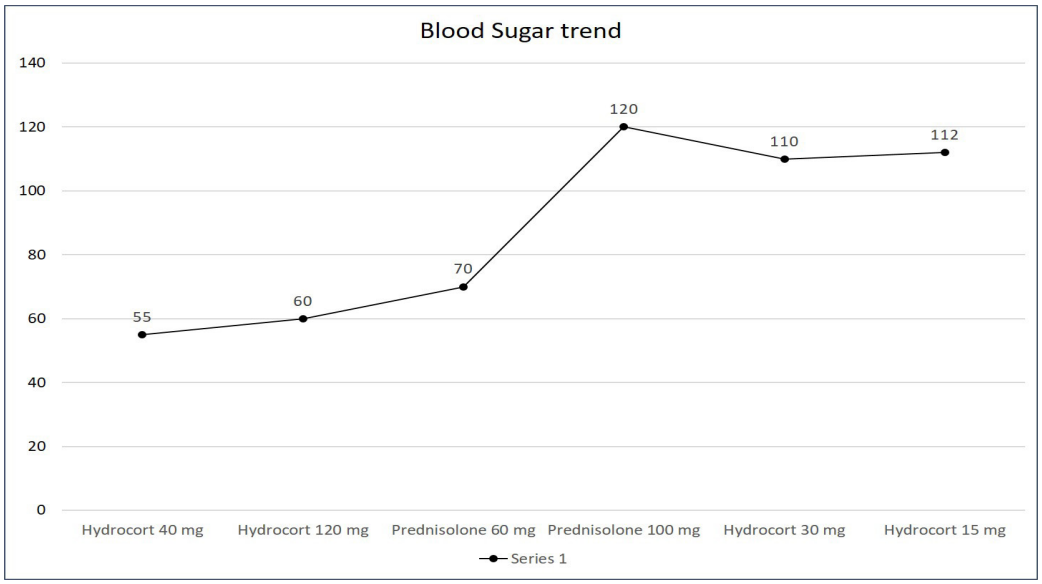

Fig. 1: Blood sugar trend

DISCUSSION

IAS–or Hirata's disease is a rare case of hyper insulinaemic hypoglycemia. This condition was first described by Hirata *et al*. in 1970.[1] It is commonly associated with other autoimmune conditions, such as Graves' disease, systemic lupus erythematosus, rheumatoid arthritis, and ankylosing spondylitis.[3]

Most patients have exposure to drugs before the precipitation of hypoglycemia. Commonly implicated drugs are methimazole, carbimazole, captopril, diltiazem, isoniazid, D-penicillamine, and alpha lipoicacid.[4]

Patients usually present in adulthood, and there is no gender predilection. Hypoglycaemic episodes typically occur in the post-absorptive state, although there can also be fasting and exercise induced hypoglycemia.[5] In our patient, fasting did not cause hypoglycemia, but it occurred spontaneously in the post-absorptive state 4-6 hours after a meal.

The mechanism of hypoglycemia in IAS is assumed to be caused by the presence of large amounts of insulin auto antibodies (IAA). After food, there is a rise in blood glucose, followed by an increase in insulin levels. Insulin is then bound by IAA, making the insulin ineffective, and leading to post prandial hyperglycemia. This triggers the production of increased amounts of insulin and C-peptide to cope with post prandial hyperglycemia. Insulin IAA complexes create a reserve of insulin: when dissociation occurs, free insulin is sustained in the post-absorptive state, leading to more prolonged and severe hypoglycemia.[5] Common differential diagnoses of IAS include insulinoma, exogenous insulin intake, and sulphonylureas. Therefore, the measurement of insulin auto antibody titre is crucial to to diagnose IAS.[6]

The molar ratio of insulin to C-peptide may be used as a marker for diagnosing IAS. The insulin to C-peptide molar ratio is less than 1 in normal individuals and in insulinoma. However, this ratio is greater than 1 in IAS and exogenous insulin administration, where C-peptide is suppressed.[7] However, in our patient insulin to C-peptide molar ratio was less than.[1]

Most cases of IAS are self-limiting, with the resolution of symptoms occurring within 3–6 months of initial diagnosis.[8]

The first line treatment includes small, frequent meals low in carbohydrates to avoid post prandial hyperglycemia and a subsequent rise in insulin. Short courses of corticosteroids (oral prednisolone 30–60 mg) may be used as adjunct therapy.[9] Other agents include acarbose (to reduce carbohydrate absorption), diazoxide, octreotide, and partial pancreatectomy (to restrict insulin release), and plasma pheresis (toreduce insulin auto antibody titers).[9] Rituximab has also been used successfully where there was a failure of response to steroids.[10]

CONCLUSION

IAS is a rare endogenous cause of hyper insulinaemic hypoglycemia. It should be suspected in any patient presenting with post prandial hypoglycemia, with high insulin and C-peptide levels. The diagnosis can be confirmed by the measurement of insulin auto antibody titers. A timely and appropriate diagnosis could avoid unnecessary investigations and abdominal exploration. Most of the cases are self-limiting, but few intractable ones require high doses of corticosteroids, dietary modifications, and steroid-sparing immune suppressants.

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