

CASE REPORTS

Autoimmune Hypoglycemia Relapse on Glucocorticoids, Effectively Treated with Azathioprine

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Abstract

Autoimmune Hypoglycemia, though very rare in India, but can be challenging to manage. Insulin autoimmune syndrome (IAS) should be considered in any patient with hypoglycemia in the setting of unsuppressed insulin levels associated with anti-insulin or anti insulin receptor antibodies. We are reporting the clinical course of one such case of insulin autoimmune syndrome, who was initially treated with glucocorticoids. The patient relapsed and was later on treated effectively with Azathioprine for glucocorticoids failure and toxicity.

Introduction

Autoimmune Hypoglycemias are rare causes of hypoglycemia. Insulin autoimmune syndrome (IAS) is the third leading cause of hypoglycemia in Japan¹, but in the India it has been rarely reported. They should be considered in any patient with hypoglycemia in the

setting of unsuppressed insulin levels associated with anti-insulin or anti-insulin receptor antibodies. In the current case study, we report the clinical course of a patient with insulin autoimmune syndrome, who was treated with glucocorticoids and later treated effectively with Azathioprine for glucocorticoids failure and toxicity.

Table 1: Laboratory parameters and management of initial episode

Dates	Insulin Level: Fasting (µIU/mL) (Fasting: 5-25)	Insulin Antibody Levels (U/mL) (Neg:<10)	FBS (mg/dl)	PPBS (mg/dl)	Remarks/ Management
8/1/2013	> 700	90.3	34-100	145	Prednisolone started 40 mg/day
23/3/2013	171	15.9	78	148	Gradual Tapering of prednisolone
02/08/2013	46	4.31	72	94	Maintenance Prednisolone 5 mg/day
10/10/2013	65.5	2.98	70	94	Prednisolone 5 mg alternate day
23/04/2014	54.54	2.26	85	143	Prednisolone stopped, Pt completely asymptomatic

Table 2: Laboratory parameters and management of relapse

Dates	Insulin level: Fasting (µIU/mL) (Fasting: 5-25)	Insulin antibody levels (U/mL) (Neg:<10)	FBS (mg/dl)	PPBS (mg/dl)	Remarks / Management
06/03/2016	>600	>100	40	134	Relapse, prednisolone restarted at higher dose 60 mg/day
30/06/2016	>600	23.5	88	153	Azathioprine 50 mg/day started and prednisolone tapered i/v/o toxicity and failure
22/08/2016	141.60	10.2	103	151	Azathioprine 50 mg/day continued. Prednisolone tapered further. No hypoglycemia
18/10/2016	6.2	61.40	108	148	No hypoglycemia, prednisolone stopped. Maintained on azathioprine only.

Case Report

A 66 year old woman, Non-Diabetic, with no comorbidities, presented with recurrent Fasting and Postprandial hypoglycemia episodes, which were biochemically proven and were relieved on consuming sweet foods or sugar. On first admission at our institute in 01/2013, Complete Hypoglycemia workup was done. Her Serum Insulin Fasting: >700µIU/mL (Fasting Range: 5-25 µIU/mL, Very High), and Insulin Antibodies: 90.3 (Normal < 10) (Strongly Positive). Insulinoma was ruled out by CECT and MRI Abdomen, and she was diagnosed as a case of insulin autoimmune hypoglycemia. She was started on Tab Prednisolone 40 mg daily. By one month her hypoglycemic attacks had stopped and the prednisolone dose was tapered down with monitoring of blood sugar levels, insulin levels, insulin antibody levels and monitoring of HPA Axis. Repeat serum insulin and insulin antibody levels showed a steady decline (Table 1).

Almost 3 years later in 03/2016, she again presented with similar episodes of Hypoglycemia with fasting insulin >600 µIU/mL and Insulin Antibodies titer >100 U/mL (Table 2). Patient was restarted on higher dose of prednisolone 60 mg/day. 3 months later her insulin level was not reduced with prednisolone and she had features of glucocorticoid toxicity, like weight gain, proximal muscle weakness etc. This time she was started with Tab. Azathioprine (50 mg) once a day. The insulin and insulin antibody levels fell, and the patient didn't have any hypoglycemia episodes. The patient tolerated azathioprine well without any

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adverse effects. The prednisolone was tapered and stopped.

Discussion

Autoimmune Hypoglycemias are rare causes of hypoglycemia.¹ The mechanism can be due to either Insulin Autoimmune Syndrome (IAS), which is also known as Hirata Disease; (having elevated levels of insulin in the presence of anti-insulin antibodies)²⁻⁴ or the hypoglycemia can be due to anti-insulin receptor antibodies having insulinomimetic action which is also known type B insulin resistance.^{2,4} The first patient with IAS was reported by Hirata et al. in Japan in 1970⁵. This condition is commonly seen from East Asian countries like Japan, Korea and Indonesia. IAS is the third leading cause of hypoglycemia in Japan,¹ (excluding insulin or other antidiabetic agents administration) after Insulinoma and Extra-pancreatic Malignancies, but uncommon elsewhere in world. It has been rarely reported in India e.g. a case associated with Monoclonal Gammopathy of Unknown Significance by Gite J et al; a case associated with ankylosing spondylitis by Raizada N et al and a case associated with pantoprazole administration by Gopal K et al. Many of the IAS patients

have recent history of medications containing a sulfhydryl group. Methimazole for the treatment of Graves' disease is the most common associated drug while less common are α -mercaptopyrionyl glycine, Glutathione, tiopronin, tolbutamide, gold thioglucose, interferon- α , D-penicillamine, penicillin G and α -lipoic acid.

Insulin autoimmune syndrome should be considered in any patient with unexplained hypoglycemia in the setting of unsuppressed insulin levels associated with anti-insulin or anti-insulin receptor antibodies. These patients have usually never been exposed to Insulin or other oral antidiabetic agents.

Up to 82% patients go into spontaneous remission,³ only stoppage of the triggering agent is required. Glucocorticoids, pancreatic surgery, plasmapheresis, azathioprine and 6-Mercaptopurine are described in literature³ for management of recurring autoimmune hypoglycemia. Glucocorticoids are one of the commonest modality used,³ and its dosages should be adjusted depending on the hypoglycemia episode frequency, serum insulin antibody and insulin

levels. Patients should be monitored for chronic glucocorticoid toxicities. They may have to be stopped in view of chronic glucocorticoid toxicity or relapse/failure during treatment. Azathioprine can effectively treat the relapse/failure cases on glucocorticoids or patients with steroid toxicity. Azathioprine as a medical management alternative, can avoid use of more invasive treatments like plasmapheresis or pancreatic surgery. Steroids can be tapered effectively and the side effects can be reversed to some extent if Azathioprine is used judiciously at right time.

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