CASE REPORT

Insulin Autoimmune Syndrome (Autoimmune Hypoglycemia)

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1. Introduction

Insulin Autoimmune Syndrome or Autoimmune Hypoglycemia, otherwise known as **Hirata's disease**, was first described by Hirata et al. in the 1970s. It is a relatively rare endocrine syndrome which features repeated episodes of Hypoglycemia, both fasting or post-prandial, with extremely high values of Insulin and C-Peptide quite unseen in any other condition. These patients can be positive for either Insulin Receptor Antibody, Anti-insulin antibody or both.

In this report, we present a case of uncomplicated, antibody-positive, auto- immune hypoglycemia, from the Government Sector in Kerala.

2. The Case

A 69-year-old female was brought to the Emergency Department with an episode of sweating, generalized weakness and fainting, in the late hours of 29th February 2020. Her blood sugar recorded on a glucometer in the Emergency was 52mg/dl. Her pupils were normal, her ECG showed no ST-T changes, a Troponin test was negative, and she had no focal neurological deficits. She was given 100ml of 25% dextrose intravenously as an infusion and her symptoms of hypoglycemia resolved in a matter of a few hours asthe blood sugar recorded 90 minutes later was 212mg/dl. It was a classical demonstration of the Whipple's triad and we admitted her to the medical general ward, for further evaluation.

She underwent a thorough history taking and physical examination in the ward. She has had no other similar episodes of hypoglycemia in the past. There was no relevant family history. She was obese as per guidelines with a BMI of 31.

We found her to have a chronic obstructive pulmonary disease, for which she was on an inhaler containing salmeterol and fluticasone propionate for the last 25 years. She also had systemic hypertension for the last 20 years, for which she was currently on Telmisartan 40mg in the morning and Cilnidipine 10mg at night. She does not give any history of being on captopril tablets anytime during the last 20 years, nor was she on any indigenous medications that could cause hypoglycemia.

She was not diabetic at any point in her life and she has not been on any form of insulin or has taken any oral hypoglycemic medications ever. We tested her HbA1c and was found to be 5.5mg%. Her Anti-GAD Antibody was tested to be normal, 8.2 IU/ml *(normal <10 IU/ml)*

Her full blood count, urine microscopy, liver and kidney function tests were all normal. Her high lipids (Total Cholesterol 276mg/dl, LDL 191mg/dl) prompted us to start her on Atorvastatin 20mg at night. A routine ultrasound abdomen and chest X-Ray PA view showed nothing significant.

The following morning, she had fasting hypoglycemia by 2 am and we found her blood sugar to be 45 mg/dl. Again, she was brought to normal by 100ml of dextrose as an intravenous infusion.

She was tested on the 6th of March 2020 for fasting Insulin and C-Peptide by the Electro Chemiluminescence Immune Assay (ECLIA) method on a COBAS 6000 analyzer at a an NABL accredited laboratory in Thiruvananthapuram and had values of 5,015 micro Units/ml *(normal 2.6 to 24.9 micro Units/ml)* and 12.5ng/ml *(normal values 1.1 – 4.4ng/ml)* respectively.

She had one more episode of hypoglycemia in the early hours of the next day when her blood sugar on glucometer was 43mg/dl. A fluoride sample sent to the lab gave a blood sugar value of 50mg/dl on Hexokinase method. We kept aside a 4ml sample of this hypoglycemic blood for serum insulin, C-peptide, ANA, anti-TPO and anti-insulin antibody assessment, later that morning. The tests gave an Insulin value of 9,914 micro Units/ml and a C-Peptide value of 20.33ng/ml which was way too higher than normal limits. Anti-Insulin Antibody results (by the ELISA method) came out a few days later and was 218 U/ml *(normal <12 U/ml)*. These raised strong suspicions of an Autoimmune Hypoglycemia.

There were three episodes of hypoglycemia where blood sugar levels were less than 50mg/dl during the stay in the hospital.

The tests, anti-TPO and

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ANA were done to check for other autoimmune possibilities, and both turned out to be negative.

The tests for beta-hydroxybutyrate and pro-insulin could not be done in the resource-limited settings of this scenario. Also, we did not feel the requirement to assess urine or serum levels of sulfonylureas as it seemed quite irrelevant in this patient.

We did a test for 5-Hydroxy Indole Acetic Acid, a marker test for a carcinoid tumour, and found it to be within normal limits.

We did a Positron Emission Tomography Scan on 14th March 2020 to rule out possible functional tumours and it returned a normal report.

A summary of important investigations

Test	Tested value	Normal Value
T3	105.5 ng/dl	80-200 ng/dl
T4	10.3 microgram/dl	4.5 -12.5 microgram/dl
TSH	1.46 micro IU/ml	0.5 to 4.7 micro IU/ml
HbA1c	5.5	less than 5.6
S. Insulin (fasting)	5,015 micro Units/ml	2.6-24.9 micro units/ml
S. C-Peptide (fasting)	12.6 ng/ml	1.1 – 4.4 ng/ml
S. Insulin *(on a blood sample with RBS 50mg/dl)*	9,914 micro Units/ml	2.6-24.9 micro units/ml
S. C-Peptide *(on a blood sample with RBS 50mg/dl)*	20.33 ng/ml	1.1 – 4.4 ng/ml
anti TPO antibody	9.73 IU/ml	upto 34 IU/ml
anti-GAD antibody	8.2 IU/ml	<10 is negative
ANA	Ratio 0.1	< 1.0 is negative
5-HIAA	4.7mg/day	upto 10mg/day is normal
8am cortisol	4 microgram/dl	10-20 microgram/dl
anti-insulin antibody	218 U/ml	>18 U/ml is positive

Given all these, viz.,

1. Recurrent fasting hypoglycemic episodes and postprandial glucose excursions
2. Presence of a high titre of insulin autoantibody
3. Presence of an unusually high titre of S. Insulin and C-Peptide on a hypoglycemic blood sample.
4. Absence of any gastric bypass surgical history in the past.
5. Absence of intake of sulfhydryl drugs
6. Non-diabetic, with no history of intake of (or abuse of) sulfonylureas.
7. Absence of any tumour, secreting insulins, on imaging.

We diagnosed this patient to have Insulin Autoimmune Syndrome (Autoimmune Hypoglycemia)

She was started on prednisolone 30mg twice a day. She did not have further episodes of Hypoglycemia. She was on regular follow up. The dose of prednisolone was maintained at 60mg per day for two months after which it was tapered to 30mg OD.

Her further test reports, nine months after the start of treatment are as follows:

1. S. Insulin **213.8 micro Units/ml** on 19th September 2020 (a decrease of 98% from the last recorded value after six months of treatment)
2. Insulin antibody – **7.6 U/ml** on 22 September 2020 (a decrease of 96.5% from the last recorded value in six months of treatment)

She last paid a visit on the 11th of November 2020 when her steroids were reduced to a bare minimal value of 10mg OD of prednisolone. She is healthy, active and has never been hypoglycemic again.

3. Discussion

Insulin Autoimmune Syndrome is a rare cause of hyperinsulinemic hypoglycemia and is of Asian origin. There are very few cases reported from other parts of the world, including India.

Insulin levels estimated on hypoglycemic blood samples are over 250 micro Units/ml with Auto-Immune Hypoglycemia. The patient discussed in this report has had almost all of her hypoglycemia

episodes while on fasting and the corresponding Insulin levels were almost 10,000 micro Units/ml.

The pathology that leads to Insulin Autoimmune Syndrome has not been fully understood. A vague theory states the formation of insulin-antibody complexes, which hinder the physiological action of insulin. Post-prandially secreted insulin gets bound to an anti-insulin antibody which prevents the availability of insulin to control hyperglycemia. This causes an additional secretion of insulin. Consequent to the decrease in blood glucose, the antibody-bound insulin is released, leading to a net increase in insulin levels in the blood, causing hypoglycemia.

Another theory stated in the literature about the mechanism of Autoimmune hypoglycemia describes a paraprotein causing hypoglycemia associated with high insulin levels and relatively low C-Peptide levels.

Autoimmune Insulin receptor disease (type B insulin resistance) could be a differential diagnosis. But, in our case, the anti-insulin antibodies were strongly positive. Moreover, our patient did not present with acanthosis nigricans and also demonstrated extremely high insulin and C-Peptide values – all of which led to the diagnosis of autoimmune hypoglycemia.

The differential diagnosis of Non-Insulinoma Pancreatogenous Hypoglycemia (NIPH) could be ruled out from history, as she has had no gastric by-pass surgeries done in the past. Moreover, it could be ruled out, as the insulin antibodies had turned out to be positive and also because no literature supports such high values of Serum Insulin with NIPH.

Insulin Autoimmune syndrome also can present with other autoimmune diseases (mostly Grave's disease). It can also be the result of the use of drugs that contain the sulfhydryl group viz., D-Penicillamine, Hydralazine, methionine, glutathione, captopril, alpha-lipoic acid, diltiazem, to name a few. Our patient did not have a history of continuous use of any of these drugs. It is believed that the interaction between the -SH (in sulfhydryl drugs) and S-S in the insulin molecule leads to allosterism of endogenous insulin, triggering an immunoreaction and causing Autoimmune Hypoglycemia. Had that been the case, a six-month drug withdrawal trial could bring about a significant reduction in the antibody titre and can reduce the frequency of hypoglycemic episodes.

Insulinoma was also considered a probable differential diagnosis. A PET Scan revealed normal reports. Moreover, the insulin and C-peptide values on a hypoglycemic blood sample have never been recorded to be over 15 times the normal (as in this case) in a case of insulin-secreting tumours. We usually see such levels only in Insulin Autoimmune Syndrome.

Her daytime sugar levels were significantly towards the higher side, indicating the alternating hyperglycemic and hypoglycemic pattern as classically seen in Autoimmune Hypoglycemia, due to the failure of insulin to bind to the receptors, causing a set-back on the physiological function of insulin.

The treatment of Insulin Autoimmune Syndrome (IAS) is targeted at eliminating the cause. Drugs causing IAS should be withdrawn. Few frequent meals and slow-release carbohydrate meals can gradually improve the patient's condition in a couple of months. As per existing literature, uncooked corn starch can be given at night at a dose of 1.5g/Kg in milk or water, to reduce the symptoms. Glucocorticoids remain the mainstay of pharmacological therapy for these patients: Prednisolone at a dose of 0.5 to 1mg/Kgbody weight can bring about a significant reduction in hypoglycemic episodes and reduce the antibody titre in a few months. The drug can be tapered and withdrawn once the insulin antibodies are tested to be negative.

In more severe or prolonged cases, we can use immunosuppressants and even plasmapheresis as a treatment modality to cure IAS. Immunoadsorption using a system loaded with sheep antigens directed against human immunoglobulin followed by two doses of 1g Rituximab has been reported effective in a patient refractory to steroids and azathioprine therapy.

Since our patient had a relatively milder condition with less frequent episodes of hypoglycemia, nutritional management with steroid support could bring about a significant reduction of symptoms.

4. Conclusion

Insulin Autoimmune syndrome is one of the rarer causes of hyperinsulinemic hypoglycemia pathophysiology of which is still poorly understood. Early suspicion of the disease in a patient with characteristic history can save unnecessary expenses in imaging and/or surgical explorations. More detailed studies about the disease can bring about a better understanding of its origin enabling healthcare providers to provide better care to a patient with IAS.

5. Bibliography

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