Case Report

Hirata Disease (Insulin Autoimmune Syndrome)- A Rare Disease Manifesting as Hypoglycemia

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Insulin autoantibodies at high titers cause hypo-glycemia episodes in patients with insulin autoimmune syndrome, commonly known as Hirata's disease. The immuno-absorbent syndrome is a type of immune-mediated hypoglycemia that arises when a trigger such as a drug or a virus) interacts with a predisposed genetic background. Insulin-autoantibodies complexes are formed during the pathophysiology of insulin autoimmune syndrome and cause double-phase glycaemic changes. Insulin is released from the complexes regardless of blood glucose concentrations, causing hypoglycemia. Insulin-autoantibodies block insulin from binding its receptor in the postprandial phase, perhaps leading to moderate hyperglycemia.[1]

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Introduction

The insulin-autoimmune syndrome is defined as developing in individuals who were not previously exposed to exogenous insulin and who do not present pathological abnormalities of the pancreatic islets. Multiple episodes of spontaneous hypoglycemia and the emergence of insulin autoantibodies without a prior history of exogenous insulin treatment are typical presenting characteristics.[2] The C-peptide level is noticeably increased, the insulin level is very high—typically up to 100 milli IU/L and the insulin antibodies are positive.[3]

Case report

A 51-year-old woman complained that she had been experiencing frequent periods of strange behavior followed by unconsciousness for the previous eight months. The patient had no prior history of drug use or chronic illnesses, including hypertension, diabetes, CAD, CVA, or any other type of chronic condition. The patient's vitals upon admission were as follows: temperature was 36.6°C, pulse rate was 88 beats per minute, and blood pressure was 120/80 mmHg. No specific neurological deficiency was present.

The woman had a history of repeated hospital stays for the same condition, but the reason for her repeated stays was never looked into.

We had retained the diagnosis of Hiratas disease because the insulin to C-peptide molar ratio has been proposed as a diagnostic tool for IAS. The insulin to C-peptide molar ratio may be theoretically reversed to higher than 1 in IAS (due to the substantially higher insulin concentrations as a consequence of the prolonged half-live on the insulin molecules that are bound in the insulin-IAA complexes).[4,5]

Discussion

Insulin autoimmune syndrome (IAS), also known as Hirata disease, represents a unique clinical entity characterized by spontaneous hypoglycemia in patients without prior exposure to exogenous insulin. Since its initial description by Hirata *et al*. in 1970, IAS has garnered increasing attention due to its distinct immunologic underpinnings and diagnostic challenges, particularly in populations with genetic

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Table 1: Investigations

USG whole abdomen	*CECT abdomen*
A Suspicion moderately defined sabermetric size (9 x7.5 mm) hypoechoic lesion noted in pancreatic head. CECT whole abdomen advised for evaluation.	No significant abnormality detected

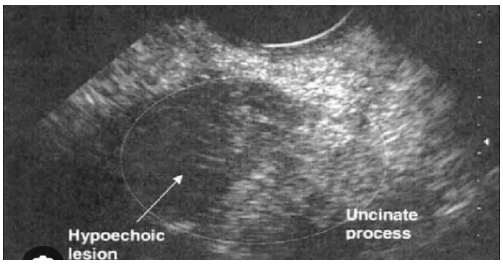

Figure 1: USG whole abdomen

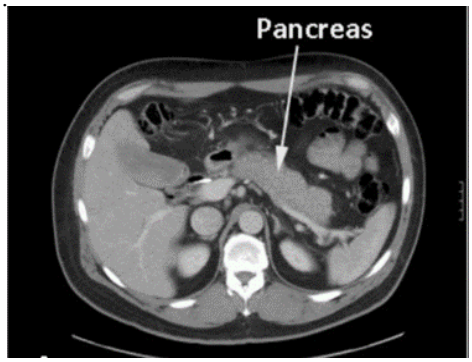

Figure 2: CECT abdomen

predispositions. A major pathogenetic mechanism in IAS is the production of autoantibodies directed against endogenous insulin. These antibodies create circulating insulin–antibody complexes that transiently sequester insulin, thereby blunting its immediate metabolic action postprandially. However, as the equilibrium shifts and free insulin is subsequently released, patients experience episodes of hypoglycemia. This biphasic phenomenon – initial postprandial hyperglycemia followed by late hypoglycemia – distinguishes IAS from other causes of hyperinsulinemic hypoglycemia such as insulinoma. Insulinoma can be ruled out by the USG abdomen (Figure 1) and CECT abdomen (Figure 2).

Clinically, IAS typically presents with recurrent episodes of neuroglycopenic symptoms—ranging from mild confusion and visual disturbances to severe seizures—often in the absence of weight loss or other systemic findings that are common in neoplastic causes of hypoglycemia. The presence of insulin autoantibodies is the hallmark of the syndrome; however, their titers and affinity can vary considerably among patients, which may affect the clinical severity and frequency of hypoglycemic episodes. Management of IAS primarily involves conservative measures. Discontinuation of the offending drug, when applicable, has been associated with spontaneous remission in many cases. In patients with persistent or severe hypoglycemia, dietary modifications with frequent, low-carbohydrate meals may help stabilize glycemic fluctuations. In select cases, short courses of corticosteroids have been utilized to reduce autoantibody production; however, the potential adverse effects of immunosuppression must be weighed against the benefits. Long-term prognosis is generally favorable, yet the risk of recurrence warrants continued clinical monitoring[5].

Table 2: Biochemical markers

CBC	11.1/8600/1.70k
ESR	14 mm/hr
RBS	67
HIV	Non-reactive
Potassium levels	4.2 mmol/L
Sodium levels	140 mmol/L
Urea	20.9
Creatinine	0.6
HBA1C	5.2%
URINE RM	WNL
T BIL	0.2
SGOT	28
SGPT	27.9
Sr.ALBUMIN	3.9

Table 3: Hypoglycaemia workup

RBS	67
FBS(6am)	51
Hba1c	5.2%
C peptide (fasting)	3.28 ng/mL
Insulin (fasting)	27.61 mIU/mL
Insulin/c-peptide ratio	>1
Insulin auto antibody	Positive

In summary, insulinoma is the disease that most frequently enters the differential diagnosis with IAS because of its higher prevalence and the underlying

similarities. In actuality, insulinomas, like IAS, are another kind of endogenous hyperinsulinemia hypoglycemia. On the other hand, IAS-induced hyperinsulinemia is significantly higher than insulinoma, and IAS-induced hypoglycemia is typically milder than insulinoma. Insulinoma can be ruled out by the USG abdomen (Figure 1) and CECT abdomen (Figure 2 and Table 1). Biochemical markers are shwon in Table 2.

The assay for IAA is the sole acceptable tool for the differential diagnosis because it is possible that insulinomas won't show up on traditional imaging examinations. Hypoglycemia resulting from exogenous insulin treatment is a type of hyperinsulinemia hypoglycemia linked to low amounts of proinsulin and C-peptide (Table 3). It is evident that this type of hypoglycemia is not connected with insulin resistance. The definitive diagnosis of sulfonylurea-induced hypoglycemia can be obtained by testing for the presence of these medications in a blood sample in IAS but absent in insulinomas. This makes the differential diagnosis more complicated when compared to other forms of drug-induced hypoglycemia, such as those caused by the administration of oral hypoglycaemic agents.[6]

Conclusion

In patients presenting with recurrent episodes of hypoglycemia, without any past drug history, Hirata's disease should be considered as a differential diagnosis after ruling out insulinoma which is a more common manifestation of hypoglycemia.[7]

Delay in the diagnosis can be avoided by a meticulous search for the underlying cause of hypoglycemia and evaluating its symptoms it.

Ethics

Written informed consent was obtained from the patient for publication.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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