Article published online: 2022-06-16

Case Report

Insulin Autoimmune Syndrome (Hirata Disease): Case Report in a Saudi Female Patient with Graves' Disease and Literature Review

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Abstract

Uncommon scenario of spontaneous hypoglycemia after starting carbimazole due to insulin autoimmune syndrome, characterized by high levels of insulinemia and circulating autoantibodies to insulin without prior insulin administration. So far, in Western countries, <70 cases have been published. In addition, more than 380 cases of this syndrome have been reported.

Keywords: Hirata disease, hypoglycemia, hypoglycemia induce by carbimazole, insulin autoimmune syndrome, insulinoma differential diagnosis, insulinoma mimics

Introduction

Insulin autoimmune syndrome (IAS) was described first by Hirata *et al*. in 1970.[1] IAS is characterized by spontaneous episodes of hypoglycemia, a high titer of insulin autoantibodies, and an increased level of immunoreactive insulin not treated previously with insulin or oral hypoglycemic agents.[1] IAS is associated with other autoimmune diseases (e.g. Graves' disease [GD], rheumatoid arthritis) and association with the human major histocompatibility complex, Class II, DR4 (human leukocyte antigen [HLA]-DR4) serotype has been demonstrated in 96% of Japanese patients with IAS.[2] There is a significant genetic predisposition to IAS (as suggested by its association with specific HLA Class-II alleles), and it is often associated with previous exposure to a drug with a sulfhydryl group in its chemical structure (e.g. methimazole, captopril). Most cases of IAS have been reported in Japan, where IAS is the third leading cause of hypoglycemia (325 patients diagnosed at the end of 2007).[1] The syndrome is rare in the Caucasian/non-Japanese populations: 60 cases in Caucasians and 20 cases in East Asians have been reported.[3,4]

Case Report

We report a 16-year-old Saudi woman not known to have any illness until she was diagnosed with GD in 2016 after palpitations, weight loss, and heat intolerance. Physical examination revealed lid lag but no exophthalmos, lid retraction, or pretibial myxedema. Laboratory investigations showed a very low level of thyroid-stimulating hormone (0.1 mlU/I), high level of free thyroxine (66.6 pmol/L) and high level of anti-thyroid peroxidase (197.9 IU/mI). Thyroid uptake scans done at that time showed high homogeneous uptake.

She was started on carbimazole (20 mg, b. d.) and propranolol as needed. After that, her symptoms subsided. Thereafter, she started to have recurrent episodes of dizziness, sweating, palpitations, and hunger pangs. These symptoms occurred once or twice a day and improved after eating sweet food. These symptoms occurred usually while she was fasting and sometimes after meals: Hypoglycemia was suspected.

Consequently, she underwent multiple investigations for hypoglycemia and was admitted to hospital for a supervised 72-h fast. During admission, results showed a high level of

Access this article online

Quick Response Code:

Website: www.jdeponline.com

DOI: 10.4103/jdep.jdep_17_19

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How to cite this article: Almutairi MZ, Aljumah HA. Insulin autoimmune syndrome (Hirata Disease): Case report in a saudi female patient with graves' disease and literature review. J Diabetes Endocr Pract 2020;3:12-4.

Received: 13-11-19 **Revised:** 07-12-19
Accepted: 02-02-20 **Web Published:** 18-07-20

c-peptide, high level of insulin, and negative urinary screen for sulfonylurea. Computed tomography and magnetic resonance imaging of the abdomen were unremarkable. The cortisol level in the morning was normal (479 nmol/L), glycated hemoglobin was 5.5%, glutamic acid decarboxylase was negative, and Islet cell antibody was negative. Table 1 provides more details about laboratory results after hospital admission.

IAS was suspected based on clinical presentation and laboratory investigations (extremely high level of insulin associated with low blood sugar, recent carbimazole use, high level of c-peptide, and unremarkable imaging findings). Insulin autoimmune antibody was measured: 0.82 nmol/L. IAS was diagnosed.

IAS can be treated by several modalities, including ≥6 low-carbohydrate meals per day to prevent postprandial hypoglycemia.[5] Some patients have been treated with corticosteroids or other medications (e.g. acarbose, somatostatin, and diazoxide) with variable results. Immunosuppressive treatment with prednisolone (30–60 mg/day) or azathioprine, or six-mercaptopurine treatment with plasmapheresis, may be an option for refractory cases.[6] The monoclonal antibody rituximab has been shown to decrease the titer of insulin autoantibodies.[7]

In our case, we used acarbose and withdrew carbimazole. Her symptoms improved, but she continued to suffer hypoglycemia. After 1 week of carbimazole withdrawal, she underwent radioactive iodine ablation. With time, symptoms started to become less frequent and eventually, stopped. The test for insulin autoantibodies was repeated and was negative. Finally, the patient became asymptomatic and required a low dose of levothyroxine.

Discussion

IAS is one of the rare causes of endogenous hyperinsulinemic hypoglycemia (EHH). IAS may be associated with autoimmune disorders such as GD, systemic lupus erythematosus, systemic sclerosis, or rheumatoid arthritis.[2,8] The exact mechanism of hypoglycemia in IAS is incompletely understood but interaction of a sulfhydryl group with a disulfide bond in the insulin molecule has been postulated to have a role.[4] Methimazole is the most commonly prescribed agent, but D-penicillamine, procainamide, isoniazid, hydralazine, glutathione, captopril, and imipenem can be prescribed. Case reports of IAS associated with the use of a-lipoic acid have been published.[9-11]

The differential diagnoses for hypoglycemia must take into account several pathologic conditions [Table 2], but diabetes mellitus-controlling medications and alcohol are considered to be the leading causes of hypoglycemia. Other well-known causes of hypoglycemia include endogenous hyperinsulinism (e.g. insulinoma, critical illnesses, and endocrine deficiencies).[12]

IAS is characterized by the presence of an autoantibody to native insulin. The autoantibody stays in the blood and binds to insulin.[2] Such binding reduces the availability of the secreted insulin to receptors in the liver and peripheral tissues, resulting in hyperglycemia and further insulin secretion. Conversely, hypoglycemia is caused by release of antibody from insulin, resulting in an inappropriately high concentration of free insulin for glucose in blood. This process of hyperinsulinemia occurs without asynchrony of the prevailing glucose concentration. This mismatch between the free-insulin concentration and blood glucose due to insulin autoantibodies is the widely accepted hypothesis for the mechanism of hypoglycemia for patients with IAS.[13] The extremely high level of insulin (>600 μIU/mL) measured in our patient favored a diagnosis of IAS. According to retrospective analyses of 84 EHH patients from 1998 to 2012 presenting at a University Hospital in Korea, the median insulin level was 14.1 μIU/mL in patients with insulinoma and >1000 μIU/mL in patients with IAS.[14] In patients with insulinoma, the serum insulin level is seldom >100 μIU/mL.[13] This increase in the insulin level found in IAS can be explained by delayed clearance of insulin as a result of insulin binding to autoantibodies.[15] C-peptide and insulin are secreted in equimolar ratios from pancreatic β-cells into the portal circulation. However, insulin is metabolized primarily in the liver and C-peptide is metabolized in the kidneys at a slower rate. The half-life of insulin is 5–15 min and the half-life of C-peptide is 30–35 min.[13] Therefore, the molar ratio of insulin: C-peptide is usually <1 even though equal amounts are secreted. This ratio is >1 in two conditions as follows: (i) IAS [as in our patient, Table 1]; and (ii) if exogenous insulin is present.[16] The molar ratio of insulin: C-peptide, C-peptide level, and insulin level in different causes of hypoglycemia are summarized in Table 3.[16] Furthermore, the criteria favoring a diagnosis of IAS are summarized in Table 4.

Conclusion

This was one of the first cases of IAS reported in Saudi Arabia/Gulf region. Even though IAS is considered one of the rarest causes of EHH, a person with EHH with an extremely high

Table 1: Laboratory results after hospital admission

	9:23 a.m.	10:29 a.m.	11:15 a.m.	12:25 p.m.
Glucose, mmol/L	7.2	3.5	2.9	1.5
Insulin, μU/mL (pmol/L)	893	376	2317 (16,090)	3653 (25,368)
C-peptide, ng/mL (pmol/L)	Not done	Not done	7.40 (2450)	11.82 (3914)
Insulin:c-peptide ratio	N/A	N/A	>1	>1

N/A: Not available

Table 2: Differential diagnoses of hypoglycemia

Drugs
Insulin or insulin secretagogs
Alcohol
Others
Critical illnesses
Hepatic, renal, or cardiac failure
Sepsis
Inanition
Hormone deficiency
Cortisol
Glucagon and epinephrine (in insulin-deficient diabetes mellitus)
Tumors not associated with pancreatic islet cells
Endogenous hyperinsulinism
Insulinoma
Functional disorders of pancreatic b cells (nesidioblastosis)
Noninsulinoma pancreatogenous hypoglycemia
Hypoglycemia after gastric bypass
Insulin autoimmune hypoglycemia
Antibody to insulin
Antibody to insulin receptors
Insulin secretagogs
Other
Accidental, surreptitious, or malicious hypoglycemia

Table 3: Insulin level, C-peptide level, and molar ratio of insulin: C-peptide in different causes of hypoglycemia

	Insulin	C-peptide	Molar ratio of insulin: C-peptide
Insulin autoimmune syndrome	↑↑↑	↑	>1
Insulinoma	↑	↑	<1
Exogenous insulin administration	↑	Suppressed	>1
Intoxication by insulin secretagog	↑	↑	<1

Table 4: Criteria favoring a diagnosis of insulin autoimmune syndrome

Very high level of insulin (>600 μIU/mL)
Ratio of insulin: C-peptide usually >1 in IAS and <1 in insulinoma
Association with autoimmune disorders or recent use of methimazole
Normal imaging
Insulin autoantibodies are present
IAS: Insulin autoimmune syndrome

level of insulin increases the suspicion of IAS. This suspicion increases even more for a patient with an autoimmune disease or who has used of a medication containing a sulfhydryl group recently. In term of IAS diagnosis, other common causes, such as insulinoma or sulfonylurea intoxication, should be excluded. Finally, hypoglycemia is one of the common complaints that should not be ignored when looking for IAS.

Acknowledgment

The authors would like to thank our Endocrine Department at Security Forces Hospital.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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