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Case Report

Autoimmune Hypoglycemia With Anti-Insulin Autoantibodies in an Eighty-One-Year-Old Woman Without Apparent Risk Factors

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ABSTRACT

Background/Objective: Insulin autoimmune syndrome (IAS) is a very rare cause of hypoglycemia presenting with recurrent fasting or postprandial hypoglycemia episodes with elevated serum insulin levels and insulin autoantibodies. The objective of this case is to highlight the importance of considering IAS in patients with hypoglycemia.
Case Report: We present a case of an 81-year-old female who presented with symptoms of hypoglycemia. She was found to have hyperinsulinemic hypoglycemic episodes without any apparent risk factors for IAS. She had positive–insulin autoantibodies in her serum leading to the diagnosis of IAS. Acutely, hypoglycemia was managed with D50 pushes, oral glucose, and glucagon injection.
Discussion: Patients who present with hypoglycemia due to endogenous hyperinsulinemia should have IAS considered as a possible differential diagnosis. Insulin autoantibodies are measured as the gold standard diagnostic test for IAS. Foods with a low glycemic index are the primary treatment for IAS.
Conclusion: This case presentation highlights the importance of considering IAS as a differential diagnosis in patients presenting with hypoglycemia secondary to hyperinsulinemia, even in the absence of apparent risk factors.

Introduction

Insulin autoimmune syndrome (IAS) also called as Hirata disease, was first reported by Hirata et al in 1970.[1] Most of the cases of IAS have been reported in Japan with only a few cases in the United States. It commonly presents in the seventh decade of life and has no association with gender. IAS is characterized by hypoglycemic episodes while fasting with high insulin levels. Additionally, patients with IAS have insulin autoantibodies or insulin receptor antibody.[2] While the pathophysiology of hypoglycemia in IAS is unknown, the most recognized mechanism is the incongruity between plasma glucose concentration and insulin levels secondary to antibodies binding either insulin or its receptor.[1] IAS commonly presents in patients with other autoimmune diseases such as Graves' disease and rheumatoid arthritis, and it is associated with HLA DR4. The diagnostic workup of IAS is aimed toward looking at causes for the hypoglycemia.[3] Majority of the patients with IAS require no treatment and undergo spontaneous remission.[2]

We present an interesting case of an 81-year-old female who presented with hyperinsulinemic hypoglycemic episodes without any apparent risk factors for IAS. She had positive–insulin autoantibodies in her serum leading to the diagnosis of IAS.

Case Report

An 81-year-old Caucasian female with a past medical history of hypertension, coronary artery disease, and congestive heart failure status post automated implantable cardioverter defibrillator (AICD)

Abbreviations: ACTH, adrenocorticotropic hormone; AICD, automated implantable cardioverter defibrillator; BHOB, beta-hydroxybutyrate; IAS, insulin autoimmune syndrome.

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placement presented with episodes of hypoglycemia, occurring mainly after meals. Her vitals at presentation were stable and within normal limits. Her physical examination was unremarkable and she had no neurological deficits. She had no history of diabetes mellitus or previous exposure to insulin or oral antidiabetic agents. The finger stick glucose on presentation was 39 mg/dL (normal = 70-100 mg/dL). A workup of refractory hypoglycemia included beta-hydroxybutyrate (BHOB), cortisol, and adrenocorticotropic hormone (ACTH) which were all within normal limits. Additionally, plasma hypoglycemic agents, including sulfonylurea and meglitinide screen, were negative. The insulin level was elevated to 1345 pmol/L (normal = 111-1153 pmol/L) with normal C-peptide of 2.64 nmol/L. A computed tomography scan of the abdomen was unremarkable and negative for a pancreatic mass. Repeat insulin levels during hypoglycemia episodes were elevated to 2247 pmol/L and C-peptide 4.14 nmol/L. Insulin autoantibody was elevated to >50.0 and insulin remained persistently elevated to 2769 nmol/L. The patient was not on any medications known to cause IAS and she did not have an acute infection triggering IAS. The patient was managed acutely with D50 pushes, oral glucose, and glucagon injection for persistent hypoglycemia. Additionally, the patient was started on steroids and continuous glucose monitoring, which eventually resolved the hypoglycemia. The patient was recommended to follow-up outpatient to discuss rituximab as an alternative management option in case of resistant disease.

Discussion

Since the first reported case of IAS in 1947, the Japanese population has had the highest prevalence of the disease, approximately 90% of the reported cases until 2009.[1] This makes IAS the third leading cause of hypoglycemia in Japan with insulinoma being the leading cause of hypoglycemia followed by extrapancreatic neoplasms.[4,5] In contrast, only 25 cases has been reported in the United States until 2014 with Caucasian ancestrory having the highest prevalence, 88%, and African American and Latin American making up the other 12%.[6] Among those diagnosed with IAS in the United States, most individuals also had other autoimmune diseases including rheumatoid arthritis, Graves' disease and/or systemic erythematous lupus.[6] However, drug-induced IAS has shown to be the most relevant among all the cases with lipoic-acid, methimazole, hydralazine, glutathione, methionine, mercaptans, clopidogrel, aurothioglucose, imipenem, penicillin G, and diltiazem.[4]

Patients with IAS could initially experience hypoglycemic attack after extraneous physical activity and present with a sudden syncopal episode. The frequency of hypoglycemic attacks may eventually increase from 2 to 4 times a year to 3 to 4 times a month at later stages of the disease.[1] Patients may also develop sudden onset of unexplained drowsiness and sweating a few hours after a meal which may resolve with sugar intake.[7] Atypical presentation may include seizure in younger patients with low serum glucose.[8] The most prominent feature of IAS is increase in serum c-peptide and insulin concentration, in a patient without history of hyperinsulinemia, during hypoglycemic attacks with further testing indicating the presence of anti-insulin antibodies.[1,7,8]

In patients with significant postprandial hypoglycemia, laboratory workup for insulin concentration along with c-peptide should be done to rule out other causes of hypoglycemia (ie, insulinoma and exogenous insulin use). In patients with insulinoma, the ratio of insulin to c-peptide is usually <1 whereas in exogenous insulin use and IAS, the molar ratio is >1.[6] The concentration of c-peptide is much lower than insulin in IAS as antibody-bound insulin molecules fail to get metabolized by the liver, whereas c-peptide is metabolized by the kidney at a normal rate. Thus patients with insulin to c-peptide ratio of greater than 1 should undergo autoimmune workup to screen for the presence of insulin autoantibodies.[6] Certain HLA subtypes, particularly DRB1*0403, DRB1*0406, DRB1*0407, and DR9, have shown to cause increased susceptibility to IAS; however, no significant association has been made up-to-date.[9]

Currently, there is no consensus on the first line therapy for IAS. Most patients with IAS have had spontaneous remission without any treatment, and in the case of drug-induced IAS, remission occurred in a few months after ceasing the use of the offending drug (ie, drugs with sulfur or sulfhydryl group).[2,4] However, administration of steroids has also shown to be beneficial due to its effect on reducing, circulating autoantibodies.[1,2] Unfortunately, relapse of IAS has been reported in patients who were treated with glucocorticoid, thus other medications such as azathioprine, rituximab, and somatostatin analog can be considered.[10-12] In terms of maintenance, it is recommended that the patients with prior diagnosis of IAS should have small but multiple meals during the day, and avoid simple sugar or food with high carbohydrate content.[1]

Highlights

- IAS presents with refractory hypoglycemia secondary to endogenous hyperinsulinemia.
- Insulin autoantibodies are measured as the gold standard diagnostic test for IAS.
- Clinician awareness of IAS can lead to diagnosis without costly imaging studies.

Clinical Relevance

Our case describes a patient with refractory hypoglycemia secondary to elevated insulin levels with positive—serum insulin autoantibodies highlighting the importance of considering IAS as a cause of hypoglycemic episodes.

Conclusions

IAS should be considered as a differential diagnosis in patients presenting with hypoglycemia secondary to hyperinsulinemia. The gold standard diagnostic test for IAS is the measurement of insulin autoantibodies. Clinician awareness of IAS can lead to prompt diagnosis without the need for costly imaging techniques or invasive surgical procedures. The first-line treatment for IAS is foods with a low glycemic index. These foods do not lead to postprandial hyperglycemia, therefore, suppressing the stimulus secretion of endogenous insulin. Additionally, steroids can be potentially added as an adjunct therapy. This case describes the classical presentation of IAS with hypoglycemic episodes secondary to elevated insulin levels and positive—serum insulin autoantibodies. Interestingly, this case had no apparent risk factors for the development of IAS.

Disclosure

The authors have no multiplicity of interest to disclose.

Acknowledgment

Informed consent: Informed consent was obtained from the patient. This manuscript does not include any patient identifying information.

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