

A Case of Insulin Autoimmune Syndrome

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Abstract

Insulin autoimmune syndrome (IAS) is a rare etiology of hypoglycemia. We present the case of a woman who was diagnosed with IAS and responded successfully to glucocorticoids. A 55 year old Hispanic woman presented with symptomatic hypoglycemia. Biochemical evaluation was notable for elevated C-peptide, insulin and pro-insulin levels. Imaging to investigate for insulinoma was negative. Insulin autoantibody titers were elevated. These findings were consistent with a diagnosis of insulin autoimmune syndrome. Glucocorticoids were started in addition to dietary modification with successful reduction in hypoglycemia episodes and insulin autoantibody titers. IAS is an immune condition characterized by insulin autoantibody-insulin complexes that spontaneously dissociate leading to hypoglycemia. The diagnosis is made by confirming elevated insulin levels with concomitant low serum glucose along with elevated insulin autoantibody levels. Treatment options include dietary modification, acarbose, glucocorticoids, plasmapheresis and rituximab. Frequent medical follow up is necessary to ensure disease remission.

Keywords: Hypoglycemia; Autoimmune; Insulinoma; Insulin

1. Introduction

Insulin autoimmune syndrome (IAS) is a rare etiology of hypoglycemia first characterized in 1970 by Yukimasa Hirata [1]. Although this condition is the third leading cause of hypoglycemia among Japanese, it is rare among other ethnic populations [2]. The main presentation of IAS is symptoms related to hypoglycemia and can vary from mild to severe with life threatening complications [3, 4]. Diagnosis can be difficult if a provider does not have high

clinical suspicion for this disease. We present a case of a Hispanic woman who presented with symptomatic hypoglycemia and was diagnosed with IAS.

2. Case Report

We present the case of a 55 year old Hispanic woman with no history of Diabetes Mellitus who presented to our hospital with two weeks of hypoglycemia. She reported symptoms of palpitations, diaphoresis and lightheadedness that would generally occur after a prolonged fast. During these episodes she had documented her blood sugar to be as low as 36 mg/dl, and these symptoms would improve following carbohydrate intake therefore confirming Whipple's Triad. She denied ingesting any oral hypoglycemic agents. She also denied consuming any over the counter or herbal supplements. She had no personal or family history of autoimmune diseases and had never experienced these symptoms previously.

During hospitalization, she had multiple confirmed blood sugars less than 60mg/dl. She was started on intravenous dextrose infusion but continued to have hypoglycemia. She had a normal cosyntropin stimulation test and thyroid function tests, thus ruling out adrenal insufficiency and thyroid dysfunction as etiologies of her hypoglycemia. Further biochemical evaluation was significant for glucose of 50 mg/dl (Ref 65-200 mg/dl), C-peptide of 12.9 ng/ml (1.1-4.4 ng/ml) Insulin level of 2808 mcIU/ml (Ref 2.6-24.9 mcIU/ml) , pro-insulin of 86 pmol/L (3.6-22 pmol/L) and undetectable beta hydroxybutyrate. Her sulfonylurea and meglitinide screen were negative. Imaging was done to evaluate for insulinoma. CT and MR Abdomen were negative for any masses. NM Octreoscan did not localize. Insulin autoantibody titer was collected which returned high at >50.0 u/ml (Ref 0.0-0.4 u/ml). She was deemed to have insulin autoimmune syndrome and was started on glucocorticoids and weaned off of the dextrose infusion. She was discharged on Prednisone 40 mg two times daily (as once daily still caused her to have hypoglycemia) along with instructions to consume frequent complex carbohydrate meals. She was given a glucose meter and instructed to check her sugar frequently. Unfortunately, due to her funding, we were not able to get a continuous glucose monitor for this patient. After discharge she has done well and is able to maintain normal blood sugars as long as she eats frequent meals. Glucocorticoids are currently being tapered and on repeat testing three months after discharge, her insulin autoantibody titer decreased to 43.7 u/ml. She is being followed closely in our Endocrinology clinic.

3. Discussion

We present the case of a Hispanic woman who was diagnosed with IAS and had a positive outcome in response to treatment with glucocorticoids. In this case, non-insulin mediated causes of hypoglycemia, including adrenal insufficiency and thyroid dysfunction were excluded with normal cosyntropin stimulation test and thyroid tests. Sulfonylurea and glinide screen were negative, thus also ruling out ingestion of oral hypoglycemic agents. Evaluation for insulinoma was unremarkable as demonstrated by a negative MR scan and Octreoscan. This patient had elevated insulin autoantibody titers therefore confirming the diagnosis of IAS.

IAS is an immunological disease characterized by large amounts of insulin autoantibodies targeted at circulating insulin molecules [5]. In this condition, insulin autoantibodies bind to insulin secreted by pancreatic beta cells after a glucose load, thus rendering insulin ineffective in the postprandial state resulting in postprandial hyperglycemia. Spontaneous dissociation of insulin from these antibodies then leads to hypoglycemia [6, 7].

The diagnosis of IAS should only be considered in a patient demonstrating all three components of Whipple's triad (symptoms of hypoglycemia with documented low glucose that improves after carbohydrate intake). The glucose level at which symptoms will present vary on an individual basis. Once Whipple's triad has been confirmed, it is imperative to obtain a detailed history including a full account of any autoimmune disorders and exposure to insulin or any other medications, along with any recent infections as IAS can be caused spontaneously or triggered by exposure to various medications, viruses or bacteria [8]. The evaluation of hypoglycemia includes a thorough biochemical evaluation to determine if hypoglycemia is insulin mediated or not. Elevated levels of C-peptide, pro-insulin and insulin levels with a concurrent low serum glucose level (<55 mg/dl) will establish the diagnosis of insulin mediated hypoglycemia. Once confirmed, it is important to investigate for all etiologies of insulin mediated hypoglycemia including sulfonylurea or glinide ingestion, insulinoma and insulin autoimmune syndrome. Insulin autoantibody titers should be measured and will be elevated in patients with IAS. In addition, IAS is more common in patients with a history of autoimmune disease.

Treatment of IAS consists of following a modified diet that includes eating frequent, small meals low in simple carbohydrates. This avoids both a prolonged fasting state and the release of large amounts of insulin from pancreatic beta cells in response to a large glucose load [2]. Continuous glucose monitoring has been reported to be a beneficial way of monitoring glucose levels in these patients [9]. In patients who continue to experience hypoglycemia episodes despite dietary changes, other treatments are available. Acarbose, although poorly tolerated due to gastrointestinal side effects, can be used to lessen the increase in glucose levels and therefore insulin levels following carbohydrate intake [10]. Glucocorticoids, namely Prednisone, has been used with success in both the reduction of hypoglycemic episodes and insulin autoantibody titers [11, 12]. In severe cases in which rapid lowering of insulin autoantibody titers are desired, plasmapheresis can be considered [13]. In addition, refractory hypoglycemia can be treated with Rituximab. Saxon et al report a case in which a 71 year old man with IAS refractory to glucocorticoids was treated with two doses of Rituximab with a successful outcome [14]. Clinical symptoms and episodes of hypoglycemia should be monitored following the diagnosis and initiation of treatment. Glucocorticoids should be tapered as tolerated to avoid complications associated with long term glucocorticoid exposure. Frequent medical follow up is important to ensure disease remission. Due to the rarity of this condition, these patients can experience a delay in diagnosis and subsequently, a delay in treatment. Thus, it is prudent for providers to have high clinical suspicion for IAS and complete a thorough evaluation in persons who present with insulin mediated hypoglycemia.

4. Conclusion

We present a case of IAS that responded to glucocorticoids. IAS should be considered in persons who present with insulin mediated hypoglycemia. Once this diagnosis is confirmed with elevated insulin autoantibody titers, multiple treatment options can be considered. Dietary modification, acarbose, glucocorticoids, plasmapheresis and Rituximab have all been used and should be considered based on the clinical situation and severity of disease. Continuous glucose monitoring is also a beneficial option in these patients. Goal of treatment is to reduce hypoglycemia episodes and induce disease remission. Frequent medical follow up is of paramount importance.

5. Disclosure

The authors have no conflicts of interest to disclose.

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