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Case Report

Insulin Autoimmune Syndrome in Graves Disease

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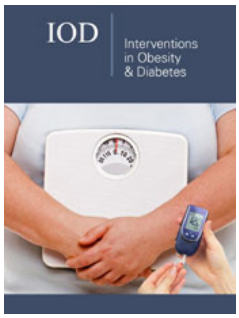

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Abstract

Insulin autoimmune syndrome is a rare cause of hyper insulinemic hypoglycaemia characterised by recurrent episodes of hypoglycaemia, elevated insulin and positive insulin autoantibodies in individuals not exposed to exogenous insulin. Approximately 80% of cases of insulin autoimmune syndrome coexist with other autoimmune diseases (Graves' disease, systemic lupus erythematosus, rheumatoid arthritis, etc.). Medications, most commonly methimazole, may cause this syndrome. The differential diagnosis should include insulinoma and type B insulin resistance. The most commonly used test for diagnosis is the insulin autoantibody test. The aim of this case report was to present the insulin autoantibody syndrome developed by methimazole in a patient with Graves' disease.

Keywords: Antibody; Insulin; Hypoglycaemia

Introduction

Insulin Autoimmune Syndrome (IAS), also known as Hirata disease, is a rare cause of hyper insulinemic hypoglycaemia characterised by recurrent hypoglycaemic episodes, high insulin and positive insulin autoantibodies in individuals not exposed to exogenous insulin. Insulin autoimmune syndrome must be distinguished from type B insulin resistance syndrome, which is caused by antibodies to insulin receptors.

It has been found that more than 50% of the 400 case reports of insulin autoimmune syndrome reviewed between 1970 and 2013 were reported from Japan, and only a few from Western countries [1]. In 50% of all IAS cases, there is a history of use of drugs containing a sulphhydryl group prior to the development of the disease. Breaking the disulfide bonds of insulin after drug use leads to an increase in the immune status of the hormone [2].

Approximately 80% of cases of IAS occur in association with other autoimmune diseases such as Graves' disease, systemic lupus erythematosus and rheumatoid arthritis [3]. Hypoglycaemia of varying severity may occur after meals or during fasting. The most commonly used test to diagnose IAS is the insulin autoantibody test.

Case Report

A 68-year-old female patient with a history of coronary artery disease, hypertension and Graves' disease presented to our outpatient clinic with complaints of palpitations, tremor and sweating, especially after meals. She was taking methimazole, clopidogrel, metoprolol and indapamide. As the patient's blood tests showed a fasting blood glucose of 78mg/dL and an insulin level of 673mu/L, the patient was measured with a 75-gram 3-hour OGTT test and simultaneous insulin measurement. The results were as follows.

OGTT	Insulin
0st Hour: 88mg/dL	524mu/L
30min: 158mg/dL	780mu/L
1st hour: 217mg/dL	1000mu/L
2nd hour: 128mg/dL	1000mu/L
3rd hour: 42mg/dL	1000mu/L

Based on these results, anti-insulin antibodies were measured. The result was positive at 92.5%. Other autoimmune diseases and multiple myeloma were excluded by tests to rule out secondary causes. Abdominal computed tomography scans showed a natural contour, dimensions and parenchymal density of the pancreas, and no space-occupying formation was detected. The patient was diagnosed with insulin autoimmune syndrome. Methimazole, the drug thought to cause this syndrome, was discontinued. Acarbose was started to delay carbohydrate absorption. She was put on a dietary programme under the supervision of a dietician. A significant reduction in the patient's symptoms was observed during follow-up. Follow-up and treatment are ongoing.

Discussion

Insulin autoimmune syndrome is a rare condition characterised by episodes of hyper insulinemic hypoglycaemia due to high levels of insulin autoantibodies. One of the two types of autoimmune hypoglycaemia is IAS and the other is type B insulin resistance caused by antibodies to the insulin receptor [4]. Methimazole and alpha-lipoic acid are the leading drugs considered to be potential risk factors for the development of IAS [5]. The fact that drugs associated with this syndrome often contain sulphhydryl compounds provides a clue to the possible pathogenesis of the disease. It is thought that these drugs break the sulphhydryl bonds between insulin chains, making the molecular structure more immunogenic [6]. Graves' disease is the most common autoimmune disease associated with IAS. This is followed by Hashimoto's thyroiditis, rheumatoid arthritis and multiple myeloma [3].

Patients with this syndrome develop hyperglycaemia as a result of insulin autoantibodies and insulin binding. Subsequently, postprandial hypoglycaemia develops due to high circulating insulin levels as a result of dissociation of the developing insulin-autoantibody complex [7]. It has been reported in the literature that insulin autoantibodies disappear spontaneously within a few months to a few years. This suggests that the disease is self-limiting. One study reported that hypoglycaemia lasted less than 1 month, whereas the average duration was 3-6 months [8]. In the first stage of treatment, it is recommended to discontinue the drug found to trigger the development of IAS and to implement dietary programmes aimed at reducing early postprandial hyperglycaemia, stimulating insulin secretion and preventing hypoglycaemic episodes [9]. Treatment with alpha-glucosidase inhibitors prevents postprandial hyperglycaemia and is therefore of variable benefit in reducing glycaemic variability in IAS [10].

Conclusion

Although IAS was first reported as a rare disease in Asian patients, awareness of the condition has increased worldwide. It is important to exclude other causes of hyper insulinemic hypoglycaemia when diagnosing IAS. The gold standard for diagnosis is the measurement of insulin autoantibodies. IAS is a self-limiting condition with a good prognosis. Once the diagnosis of IAS has been confirmed, if there is an agent that is thought to cause the pathogenesis, it should be discontinued, and diet should be recommended as supportive treatment. Pharmacological treatment may include acarbose to delay glucose absorption or, in patients with severe symptoms, somatostatin, immunosuppressive agents or even plasma exchange to remove autoantibodies from the body.

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