METHIMAZOLE-INDUCED INSULIN AUTOIMMUNE SYNDROME IN GRAVES’ DISEASE: CASE REPORT

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ABSTRACT

Insulin Autoimmune Syndrome (IAS) is a rare cause of hypoglycemia. We present the case of a 54-year-old male patient who was admitted to the emergency department with blurred consciousness approximately 6 weeks after the initiation of the methimazole therapy due to the diagnosis of Graves’ disease. The blood glucose level was 40 mg/dL and levels of fasting insulin, C-peptide, and anti-insulin antibodies were increased. The patient was considered to have IAS and the methimazole therapy was terminated. Following the termination of the treatment, the complaints disappeared and the insulin antibodies gradually decreased to normal levels in approximately 8 months.

Key words: Hypoglycemia, Insulin autoimmune syndrome, Methimazole.

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Introduction

Insulin autoimmune syndrome (IAS) was first described by Hirata et al. in 1970 as a disease characterized by increased levels of insulin antibodies associated with hypoglycemia4. The prevalence of IAS is remarkably high in Japan5. IAS is accompanied by an autoimmune disease in most of the patients, such as Graves’ disease, Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA) and chronic hepatitis3. Patients with a diagnosis of Graves’ disease and those who are treated with methimazole, which contains a sulfhydryl group, show a high risk of IAS development6. The insulin antibodies probably develop as a result of an immunologic and chemical reaction between insulin molecules and these sulfhydryl groups, thereby leading to the development of IAS3.

In this report, we present a case who was admitted to our emergency department with hypoglycemia attacks approximately 6 weeks after the initiation of methimazole therapy due to the diagnosis of Graves’ disease. The patient showed a full recovery due to the termination of the methimazole therapy following the diagnosis as IAS.

Case presentation

A 54-year-old male patient was admitted to our emergency department with diaphoresis, palpitations, and blurring of consciousness. Blood glucose level was 40 mg/dl and the patient was hospitalized at our clinic for the investigation of the etiology of hypoglycemia. Approximately 6 weeks prior to admission, the patient had been diagnosed as having Graves’ disease and was initiated on
methimazole 20 mg/day. Patient history revealed that the complaints of diaphoresis, palpitations, and fatigue had started approximately 2 weeks after the initiation of the methimazole therapy and were aggravated particularly during fasting periods. The patient had no personal or family history of diabetes and was not using any oral antidiabetic medication or insulin. He had a 30-year history of smoking (1 pack/day) but was not using alcohol or any other substance. Additionally, he had no family history of autoimmune diseases or endocrinological diseases such as neoplastic diseases. On physical examination, the thyroid gland was palpable with stable vital functions, and the patient did not have exophthalmoses. Liver and kidney function tests of the patient were in normal ranges. Other laboratory findings are reported in Table 1.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Laboratory findings were as follows. ACTH: Adrenocorticotropic Hormone; anti-TPO: Thyroid Peroxydase Antibody; FBG: Fasting Blood Glucose; fT4: Free Thyroxine; fT3: Free Triiodothyronine; HBA1C: Glycosylated Hemoglobin; TSH: Thyroid Stimulating Hormone</th>
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<tbody>
<tr>
<td></td>
<td>Normal range</td>
</tr>
<tr>
<td>FBG (mg/dl)</td>
<td>74-106</td>
</tr>
<tr>
<td>HBA1C (%)</td>
<td>4.6-6.1</td>
</tr>
<tr>
<td>ACTH (mcg/dL)</td>
<td>0.46</td>
</tr>
<tr>
<td>Cortisol (mcg/dL)</td>
<td>2.3-19.5</td>
</tr>
<tr>
<td>TSH (uIU/mL)</td>
<td>0.34-4.2</td>
</tr>
<tr>
<td>fT4 (ng/dL)</td>
<td>0.61-1.1</td>
</tr>
<tr>
<td>fT3 (pg/mL)</td>
<td>0.06-1.1</td>
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</table>

The insulin antibody levels, total insulin levels, and fasting glucose levels were followed up after the termination of the methimazole therapy. The level of insulin antibodies gradually decreased to normal levels in 8 months (Table 2). HLA-DRB1*0406 and HLA-DQB1*0302 alleles were positive. No complaints or physical examination findings of SLE, RA, or chronic hepatitis associated with IAS were found.

The patient was negative for hepatitis markers, antinuclear antibody (ANA), and rheumatoid factor (RF). The patient was administered 15 mCi RAI therapy due to the presence of Graves’ disease. The thyroid function tests regressed to normal levels after 1 month.

**Discussion**

Insulin autoimmune syndrome (IAS) was first described by Hirata et al. in 1970(6). IAS is a syndrome characterized by the presence of hyperinsulinemia, insulin antibodies and hypoglycemia in individuals who were never exposed to insulin or any oral antidiabetic medication. This syndrome generally presents after the 4th decade and its incidence is equal in males and females(8). IAS is rarely seen in the Western countries, whereas its prevalence is remarkably high in Japan and more than 380 cases have been reported in the literature. Moreover, it is the 3rd most common cause of hypoglycemia in Japan(3). IAS should be considered in patients suspected with an insulinoma, in order to avoid unnecessary invasive interventions, costly applications, and surgery.

IAS is accompanied by other autoimmune diseases such as SLE, RA, and chronic hepatitis approximately in 80% of the patients(3). Nearly 50% of the patients with IAS have a history of exposure to a medication, particularly to a medication that contains a sulfhydryl group such as thionamides (methimazole, carbimazole, propylthiouracil), captopril, penicillamine, pyritinol, imipenem,
Methimazole-induced insulin autoimmune syndrome in Graves’ disease: case report

Some medications used in the treatment of diabetic neuropathy, which is a popular medication used in the treatment of diabetic neuropathy, has been reported to be a cause of IAS(8). Moreover, among the medications reported to be a cause of this syndrome, methimazole is the most frequently reported drug. Hypoglycemia may present at fasting or as a reactive hypoglycemia in both ways in IAS(8). Our patient was a 54-year-old man who had symptomatic hypoglycemia episodes particularly during fasting periods and had a history of exposure to methimazole for 6 weeks due to the diagnosis of Graves’ disease. The patient had no other accompanying autoimmune diseases such as SLE, RA, or chronic hepatitis.

Graves’ disease does not pose a risk for IAS by itself. In a study, 206 patients treated with methimazole, 118 patients taking propylthiouracil for Graves’ disease, and 118 untreated patients were compared in terms of insulin autoantibody development, and autoantibody were found only in 6.3% of the methimazole group(9).

Although the exact pathogenetic mechanism of IAS remains unknown, the most widely accepted theory suggests the presence of discordance between bound and free insulin forms that occur secondary to insulin antibodies. Insulin concentration in blood increases after meals or oral glucose tolerance testing (OGTT). Autoantibody binding to insulin receptors inhibits the effects of insulin, causing postprandial hyperglycemia. This temporary hyperglycemia may be the cause of high glycosylated hemoglobin (HbA1c) levels seen in some patients with IAS. Gradually, insulin molecules separate spontaneously from the antibodies and cause hypoglycemia by creating disproportionately high insulin levels when compared to plasma glucose(10). Insulin antibodies with a high binding capacity and a low affinity are probably responsible for these hypoglycemic episodes(11). The mechanism of hyperinsulinemia in IAS may be explained as follows: binding of insulin secreted from the pancreatic β-cells by insulin antibodies causes a relative insulin deficiency, which in turn causes an inappropriate insulin secretion from the pancreatic β-cells and an increase in insulin levels by causing a delayed clearance(10). Presence of islet cell hyperplasia has been shown in these patients in histologic studies(12). Another striking characteristic of IAS is an insulin level of >1,000 pmol/L, which occurs secondary to insulin molecules bound to insulin antibodies(13).

However, this high insulin level is rarely present in patients with insulinoma(10). Free insulin levels may be normal or increased, along with increased C-peptide and proinsulin levels(10). The insulin level of our patient (>1,000 μU/mL) and the C-peptide levels were increased at diagnosis; however, the levels of free insulin and proinsulin could not be measured.

C-peptide and insulin are secreted in equimolar ratios, from the pancreatic β-cells into the portal circulation. On the other hand, insulin is primarily metabolized in the liver and C-peptide is metabolized in the kidneys at a slower rate. Half-life of insulin is 5-15 minutes and half-life of C-peptide is 30-35 minutes(14). Therefore, the molar ratio of insulin/C-peptide is normally <1, although equal amounts are secreted. This ratio is >1 in two conditions. The first is IAS and the second is presence of exogenous insulin(14). The insulin/C-peptide molar ratios and the C-peptide and insulin levels in different causes of hypoglycemia are summarized in Table 3(14).

<table>
<thead>
<tr>
<th></th>
<th>Insulin</th>
<th>C-Peptide</th>
<th>Insulin/C-Peptide Molar Ratio</th>
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</thead>
<tbody>
<tr>
<td>Insulin autoimmune syndrome</td>
<td>↑</td>
<td>↑</td>
<td>&gt; 1</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>↑</td>
<td>↑</td>
<td>&lt; 1</td>
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<tr>
<td>Exogenous insulin administration</td>
<td>↑</td>
<td>Suppressed</td>
<td>&gt; 1</td>
</tr>
<tr>
<td>Insulin secretagogue intoxication</td>
<td>↑</td>
<td>↑</td>
<td>&lt; 1</td>
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Table 3: Insulin, C-peptide and Insulin to C-peptide Molar Ratio in different causes of hypoglycemia.

In our patient, the insulin level was 1,050 μU/mL (7,292.25 pmol/L) after dilution and the simultaneous C-peptide level was 8.2 ng/mL (2,714.2 pmol/L), with an insulin/C-peptide molar ratio of 2.6, which is consistent with IAS. Eight months after the termination of the treatment, the insulin level with methimazole was 5.4 μU/mL (37.5 pmol/L) and the simultaneous C-peptide level was 1.12 ng/mL (370.72 pmol/L), with an insulin/C-peptide molar ratio of 0.1, which was considered normal (normal value, <1).

Methimazole is a drug which is a member of the imazol thionamide group and is frequently used for the treatment of hyperthyroidism. Thionamides have various minor side effects and some serious side effects which may be life-threatening (table 4).
IAS is a rare, serious side effect of thionamides. The molecular mechanism of methimazole-induced IAS is associated with the sulfhydryl group of methimazole. The natural structure of insulin is disrupted due to an interaction between the disulfide bonds in the insulin molecules and the sulfhydryl groups of methimazole, thus leading to the development of antibodies. Insulin-derived peptides, which develop as a result of the disruption of the natural insulin structure, are recognized by antigen-presenting cells and activate the T-cell-mediated immune system. Almost half of the patients diagnosed as IAS have a history of exposure to a medication containing a sulfhydryl group. The prevalence of methimazole-induced IAS is remarkably high in Japan. To date, a total of 64 cases have been reported from Japan, 16 cases from Eastern Asia, 5 cases from Korea, and 2 cases from the Caucasus. To the best of our knowledge, no cases have been reported from Turkey. Therefore, our patient is the first IAS case to be reported from Turkey.

Presence of a close association between HLA genotypes and IAS is commonly accepted in Japan. Polyclonal insulin antibodies are observed in most of the patients with IAS and there is a close association between HLA-DRB1*0406, DQB1*0302 and DQA1*0301. Frequently, these HLA alleles are associated with increased prevalence of IAS compared to the general population in Japan. The association between HLA genes and methimazole-induced IAS has been detected only in Japan.

However, a case of methimazole-induced IAS who was positive for HLADRB1*0406 was also reported in Korea in 2013. In our study, HLA genotyping was performed by low-resolution HLADR typing and was carried out according to the manufacturer’s specification for LABType SSO (One Lambda Inc, USA), and the retrieved output was analyzed by HLA Fusion v 1.2.1. software (One Lambda Inc, USA) for allele identification. HLA genotyping was performed by reverse sequence-specific oligonucleotide and the result was HLA-DRB1*0406 and HLA-DQB1*0302.

Hypoglycemia resolves spontaneously in approximately 3 months in nearly 80% of patients after the termination of the treatment with the medication suspected to cause IAS. The recommended treatment for methimazole-induced hypoglycemia includes the termination of this medication and a low-carbohydrate consisting of 6 or more meals in a day. Alpha-glucosidase inhibitors decrease the secretion of insulin from the pancreatic β-cells by reducing the glucose absorption from the intestines and may play a role in the treatment of IAS. If the hypoglycemia is resistant, immunosuppressive treatment with prednisolone 30-60 mg/day or azathioprine or 6-mercaptopurine treatment with plasmapheresis may be tried. Moreover, another CD20 monoclonal antibody, rituximab, is known to decrease insulin autoantibodies.

Therefore, this antibody may be effective by decreasing the insulin antibodies in the treatment of resistant hypoglycemia in methimazole-induced IAS. In our patient, no hypoglycemic episodes were observed 1 week after the termination of the methimazole therapy and the initiation of a low-carbohydrate diet containing 6 meals a day. In addition, the insulin, C-peptide, and insulin antibodies gradually decreased in 6 months and returned to normal levels.

**Conclusion**

Methimazole is a medication frequently used for the treatment of hyperthyroidism. Methimazole-induced IAS should be considered in patients with hypoglycemia, which occurs after exposure to methimazole. Complete recovery is obtained in 80% of the patients after the termination of methimazole therapy. IAS is a rare cause of hypoglycemia. Insulin antibodies should be investigated in patients suspected of insulinoma in order to avoid unnecessary invasive interventions and
surgery, especially if insulin levels are very high to rule out IAS.

References