Insulin Autoimmune Syndrome Possibly Caused by Alpha Lipoic Acid

Yuichiro Takeuchi, Takahide Miyamoto, Tomoko Kakizawa, Satoshi Shigematsu and Kiyoshi Hashizume

Abstract

Insulin Autoimmune Syndrome (IAS) is a rare disease characterized by hypoglycemia and autoantibodies to insulin without prior insulin administration. Here, we report a case of IAS associated with alpha lipoic acid (ALA). The patient is a 55-year-old man. He began to complain of hypoglycemic symptoms after taking ALA. He lost consciousness in the late postprandial period and blood glucose was found to be 27 mg/dl. A high insulin level and high titers of insulin antibodies were detected. His HLA genotype contains DRB1*0406. As ALA comes to be used widely, the incidence of IAS due to ALA might increase.

Key words: insulin autoimmune syndrome, alpha lipoic acid, anti-insulin antibody, HLA DRB1*0406

Introduction

Insulin autoimmune syndrome (IAS) was first reported in 1970 by Hirata et al (1). This syndrome is a condition characterized by frequent hypoglycemic attacks associated with the presence of autoantibodies to insulin in patients who have not received insulin injections. More than 200 IAS patients have been reported in Japan where it represents the third leading cause of spontaneous hypoglycemia (2); only 27 cases have been described from outside Asia. Forty-one percent of Japanese patients with IAS had other autoimmune diseases such as Graves’ disease and rheumatoid arthritis. A strong association between IAS and HLA DR4 has been shown in 96% of Japanese patients (HLA DR4 frequency is 43% in normal Japanese controls) (2). Analysis of the nucleotide sequences indicated that the haplotype of patients with IAS is DR B1* 0406, DQ A1* 0301 and DQ B1* 0302 (present in all patients and in 14% of controls) (3). The DR B1* 0406 allele appears to play an important role in presenting insulin peptides to T cells. The susceptibility haplotype is present in the Japanese population, which may account for the high frequency of IAS. There is a strong correlation between HLA DRB1* 0406 and IAS (2, 3).

The role of drug-induced autoimmunization has been suggested since drugs containing the sulphydryl group (i.e. thiamol, methimazol, D-penicillamine, tiopronin or glutathione) were administered in 50% of cases 4 to 6 weeks before the onset of hypoglycemic attacks (4, 5). In most cases, insulin autoantibodies appear a few weeks after the beginning of treatment with a drug containing the sulphydryl group (5, 6). A significant increase in insulin and C-peptide plasma concentrations and the presence of other an- tiorgan antibodies are observed. Here, we describe a case of IAS that was triggered by alpha lipoic acid (ALA).

Case Report

A 55-year-old man was referred to our hospital in early December 2005 to determine the cause of frequent hypoglycemia. He had a history of obesity, hypertension and hyperuricemia for several years. He had gradually gained weight to become around 100 kg. Previously, the therapeutic administration of ALA (225 mg/day) had been started for diet purposes. A week later, he began to complain of repeated episodes of hunger, sweating, palpitations and tremor. The symptoms disappeared after the ingestion of food such as sweets, and he gained weight (by 1-2 kg/month). In the evening of November 25, he lost consciousness and was brought to an emergency hospital. His blood glucose level was 27 mg/dl, and the administration of glucose restored his consciousness. His fasting blood glucose level was 57 mg/
In early December 2005, he was referred to our hospital in order to examine for the cause of hypoglycemia. The patient had never received medications such as insulin, antithyroid drug, glutathione, or D-penicillamine, all of which are known to elicit antibodies to insulin. Physical examination revealed an alert man in apparently good health. His height was 179 cm, weight 103 kg, pulse rate 75/min, and blood pressure 124-88 mmHg. Laboratory findings showed normal results in the blood cell count, blood chemistry, endocrinological studies and urinalysis except for slight liver dysfunction (AST 73 IU/l, ALT 109 IU/l, γ-GTP 192 IU/l) and hyperuricemia (UA 9.3 mg/dl). Serologic examination was unremarkable: tests for C-reactive protein, rheumatoid factor, antinuclear antibodies, anti dsDNA antibodies and anti-thyroid antibodies were all negative. Serum immunoglobulin G, A and M levels were also within the normal ranges. Anti-GAD antibody and anti-IA2 antibody tests were negative but high titers of insulin antibodies (93.3%: normal range 7%) were found. An oral glucose tolerance test performed over 240 min showed a basal glucose value of 67 mg/dl, with a peak of 140 mg/dl at 30 min and a nadir of 38 mg/dl at 240 min. Plasma insulin ranged from a basal level of 191.6 μIU/ml to a peak level of 1005 μIU/ml at 120 min (normal range 5-25 μIU/ml). Basal C-peptide levels were 13.2 ng/ml (normal range 1.5-3.6 ng/ml)(see Table 1). Attempts at tumor localization (abdominal computed tomodraphy scan and abdominal nuclear magnetic resonance) failed to identify the locus. The diagnosis of IAS was made. HLA types were A* 0207, A* 2402, B* 5101, B* 5201, Cw* 1202, Cw* 1402, DRB1* 0406 and DRB1* 1502. He was advised to fractionate his meals and the symptoms gradually disappeared within a few weeks. Serum insulin levels and titres of anti-insulin antibodies during follow-up are shown in Fig. 1.

Table 1. Results of 75 g Oral Glucose Tolerance Test

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>120</th>
<th>180</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td>BG (mg/dl)</td>
<td>67</td>
<td>140</td>
<td>136</td>
<td>119</td>
<td>88</td>
<td>38</td>
</tr>
<tr>
<td>IRI (μIU/l)</td>
<td>191.6</td>
<td>250.1</td>
<td>311.4</td>
<td>1005.0</td>
<td>994.6</td>
<td>296.5</td>
</tr>
<tr>
<td>CPR (ng/ml)</td>
<td>13.2</td>
<td>17.2</td>
<td>17.2</td>
<td>18.4</td>
<td>14.8</td>
<td>13.3</td>
</tr>
</tbody>
</table>

Discussion

Here, we report a case of insulin autoimmune syndrome possibly caused by alpha lipoic acid. IAS was suspected in this patient because hypoglycemia was present in association with extremely high levels of serum insulin. The hypoglycemia probably results from the dissociation of insulin from its antibodies, several hours after meals, when no further absorption of glucose is occurring (7). Actually, hypoglycemia occurred in the late postprandial period and not during fasting in our patient. Scatchard analysis seemed to be useful to understand the correlation between anti-insulin antibody and hypoglycemia, but it was difficult to perform due to the few samples remaining in our hospital. Because he was obese, it also seemed that he had insulin resistance and hyperinsulinemia from the beginning. However, it could not account for the extremely high level of serum insulin in this case. Moderately increased CPR levels are also reported in most of IAS patients. Anti-insulin antibodies may affect the measurement of CPR. So in this patient, the cause of hypoglycemia in the postprandial period was thought to be mainly insulin autoimmune syndrome. One month before IAS was diagnosed, he had taken ALA (215 mg/day) to diet. The role of drug-induced autoimmunization has been suggested since drugs containing the sulphydryl group (i.e. thiamazol, methimazol, D-penicillamine or glutathione) were administered in 50% of cases 4 to 6 weeks before the onset of hypoglycemic attacks. In most cases, insulin autoantibodies appear a few weeks after the beginning of treatment with a drug containing the sulphydryl group (4-6). Also imipenem and penicillin G, beta-lactam antibiotics which generate sulphydryl groups, have been recently implicated in the pathogenesis of cases of IAS (4, 8, 9). Very interestingly, these agents which are known to elicit IAS possess of sulphydryl groups in their structures and have a reductive effect.

It is thought that there is a strong association between specific HLA allele and IAS. Japanese IAS patients are DR4 positive in 96% (49 out of 51) of cases, possessing either DRB1* 0406 (42 cases). DRB1* 0403 (5 cases) or DRB1* 0407 (1 case) in the polyclonal type, and DRB1* 0405 in the monoclonal case (2). In fact, the present patient possessed DRB1* 0406. It turned out that the motif of Ile-Leu-Gln has a high affinity for DRB1* 0406 molecule. The α chain of insulin contains this amino acids’ motif (4). Additionally it was clarified that some of α chain of insulin (TSICSLYQLE, 8-17th amino acids) show a high affinity.
Figure 2. The structure of alpha lipoic acid (ALA). Two sulfur atoms exist side by side in ALA, and its unique structure produces the strong reductive effect.

for DRB1*0406 molecule. Moreover, it was noted experimentally that this peptide strongly stimulates T cells derived from a DRB1*0406 positive patient (10-12). These findings suggest that this insulin-derived peptide is possibly presented to T cells by antigen presenting cells such as macrophages, and it develops IAS in HLA DRB1*0406 positive patients. Interestingly, a loop is formed by S-S bond in α chain of insulin over this motif (4). And by reductive effect, medicines possessing sulphhydryl groups seem to expose this motif to antigen presenting cells by promoting dissociation of S-S bonds of insulin molecule.

ALA has a strong reductive effect, which is 400 times as strong as vitamin C or vitamin E. Though ALA is taken from food products such as spinach and liver, the amount of ALA intake is limited. It is noteworthy that ALA also possesses two sulfur atoms in its structure and has a unique characteristic in that it has strong antioxidative, a reductive effect (see Fig. 2) (4). In Europe and U.S.A., ALA has been used for diabetes mellitus and dieting. In Japan, ALA had been taken by patients of subacute necrotic encephalopathy and toxic hearing disturbance, and it has been admitted to be taken as a health supplement since June 2004. For the strong antioxidative effect, ALA has come to be used widely as a health supplement for dieting and antiaging in Japan. In fact, another case of IAS possibly caused by ALA was reported (13). A relatively high frequency of HLA DRB1*0406 (3.22%) in Japanese was described (14). Given that ALA has come to be widely used as a health supplement, it will be important to be more careful to watch for the development of IAS connected with ALA.

References