Insulin Autoimmune Syndrome after the Third Therapy with Methimazole

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In 1986, a 26-year-old female had been diagnosed as having Graves’ disease and had been treated with methimazole for four months. After the treatment with propylthiouracil for another four months, she had been treated with methimazole once again. She was in complete remission for two years. She again experienced symptoms of hyperthyroidism, and treatment with methimazole was started again. On the thirteenth day after treatment, she experienced hypoglycemic attacks with skin eruption. The plasma glucose was 57 mg/dl, 125I-Insulin binding 69%, free IRI 196 μU/ml. The patient had the HLA-DRB1*0406.

Introduction

Since the first report of insulin autoimmune syndrome by Hirata and colleagues in 1970, 244 cases have been reported throughout the world (1-4). This syndrome is characterized by spontaneous hypoglycemia, hyperinsulinemia and auto-antibodies to insulin without previous immunization. The recent report by Uchigata and colleagues has identified specific HLA antigens strongly linked to the development of this syndrome (5). Certain drugs, such as methimazole, which have sulphydryl groups trigger this syndrome, but little is known about the mechanisms of this autoantibody production. These drugs induce the syndrome after rechallenge with the same drug in some cases (6-13). We treated a patient with Graves’ disease who presented with this syndrome after the third treatment of methimazole. This case strongly suggested that the priming effect is important in this drug-induced autoimmune phenomenon.

Case Report

A 26-year-old female visited our hospital because of palpitation and weight loss in November 1986. Three years earlier the patient was diagnosed with Graves’ disease and had been treated with methimazole for four months. Methimazole was changed to propylthiouracil because she wanted to become pregnant and the treatment was continued for four months. Since she did not become pregnant she was treated with methimazole once again. Symptoms of hypoglycemia, eruption or abnormal liver function tests had not been elicited during these treatments. The patient entered complete remission and the drugs were not necessary for two years. She delivered her first child in April 1989. She visited our hospital because of palpitation and finger tremor in November 1989. Her presenting symptoms suggested the relapse of Graves’ disease. The laboratory findings showed high levels in plasma triiodothyronine (T3), 3.3 ng/ml and thyroxine (T4), 14.5 μg/dl concomitant with suppressed thyroid-stimulating hormone (TSH) as below 0.1 μU/ml. TSH receptor antibody was positive (22.3%) and 123I thyroidal uptake was high (61.2% at 24 hours).

Treatment with methimazole was resumed, and eleven days later, she transiently complained of urticaria after taking a bath. Thirteen days later, she noticed a cold sweat, palpitation, finger tremor, and thirst before lunch.

These symptoms disappeared after intaking sugar. This attack occurred again at fasting and then she visited our hospital. Her height was 156 cm, and she weighted 48 kg. Her temperature was 36.4°C, pulse 84 per minute, and blood pressure 98/60 mmHg. Exophthalmos was noted bilaterally. The thyroid was diffusely enlarged without tenderness. The heart, lung and abdomen were normal. The results of urinalysis were normal. Laboratory findings were as follows; plasma glucose,
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57 mg/dl; $^{125}$I-insulin binding, 69%; free IRI, 196 μU/ml; total IRI, 19,038 μU/ml; C-peptide, 33 ng/ml.

Insulin autoantibodies were mainly IgG with kappa type light chains. Scatchard analysis of insulin autoantibodies in this case showed the characteristic binding site with lower affinity and higher capacity for insulin than those of insulin-treated cases (Fig. 1). HLA typing of the patient showed A2, A26 (10), BW62 (13), BW61 (40), CW4 and DR4. Analysis of the nucleotide sequence of the DR showed DRB1*0406, DQAl*0301, DQB 1 *0302. The treatment with methimazole was continued, and hypoglycemic attacks disappeared after a week (Fig. 2).

**Discussion**

Insulin autoimmune syndrome was first reported and has ethnic preponderance in Japan (1-4). The studies of this syndrome have been increasing, but its pathogenesis remains unclear. Some drugs which have sulphydryl groups such as methimazole are closely related to this syndrome (6-16). Nineteen cases of this syndrome have been reported in patients with Graves' disease treated with methimazole (6-13). Fifteen of them had hypoglycemic attacks after the initial treatment with this drug, four had the attacks after rechallenge with the same drug. However, no cases developed this syndrome after the third treatment with methimazole as the present case. HLA typing and analysis of the nucleotide sequence of the DR genes in this case revealed similar types which are characteristic in this syndrome (4, 5, 17-20). Therefore, the background in this case for generating insulin autoantibodies may be the same as that in other cases. The scatchard plots of insulin autoantibodies in this case showed two binding sites with high and low affinity. The affinity of the high affinity constants was lower than that of insulin-treated cases. On the other hand, the capacity was larger than those insulin-treated cases (18). Hence, we suggested that large volume of insulin released from these antibodies might lead to hypoglycemia. It is not clear why hypoglycemic attacks appeared only when methimazole was administered for the third time, and not after the second time in this case. Unfortunately we failed to examine the titer of insulin autoantibodies at the first and second therapy with methimazole. The appearance of insulin autoantibodies may have occurred without hypoglycemia during these periods (21). In addition to genetic predisposition, other acquired autoimmune abnormalities such...
as a relapse of Graves’ disease and pregnancy might have promoted the production of insulin autoantibodies. In spite of maintaining the methimazole therapy, the hypoglycemia disappeared and the titer of insulin autoantibodies was decreased. These findings suggested that the production of insulin autoantibodies might depend on the dose of methimazole. All previous patients with this syndrome (with hypoglycemia) triggered by methimazole therapy were given large doses of methimazole (30 or 40 mg/day). On the other hand, in the present case methimazole was given in small doses (5 mg/day) during the second therapy. The accumulative dose of methimazole up to the onset of symptoms was about 6 g in this case. It is impossible to speculate whether there is a critical dose because not all case reports discussed the dose of the drug. However, it seems likely that there may be a dose-dependent relationship between the generation of insulin autoantibodies and methimazole. Further studies of this syndrome will be necessary to resolve this question.

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References