Myasthenia Gravis Associated with Graves' Disease in Japan

Mariko Ohno, Noboru Hamada, Junichi Yamakawa, Jaeduk Noh*, Hirotoshi Morii, and Kunihiiko Ito*

The prevalence of myasthenia gravis in Graves' disease was 0.14% in the 22,956 patients with Graves' disease who came during 1968-1979 to the Ito Hospital, Tokyo. While age at the onset of Graves' disease in patients with myasthenia gravis was slightly lower than that in those with Graves' disease without myasthenia gravis, age at the onset of myasthenia gravis in patients with Graves' disease was not different from that of myasthenia gravis patients without Graves' disease. Of 33 patients with both myasthenia gravis and Graves' disease, 8 developed myasthenia gravis first, 13 developed Graves' disease first, and in 12 the two diseases occurred concurrently. Most patients in whom Graves' disease developed first had clinical manifestations of myasthenia gravis within 2 years of the onset of Graves' disease. The dosage of an anticholinergic drug required to control symptoms decreased as the thyroid function was normalized, and no cases showed the "see-saw phenomenon."

Key Words: Hyperthyroidism, Anticholinergic drug, See-saw phenomenon

It is known that myasthenia gravis and Graves' disease coincide frequently. In Western countries, Ossermann and Silver1 reported that the prevalence of myasthenia gravis in Graves' disease was 0.35% and Simpson2 found it was 0.20%. Sahay et al.3 reported it as 0.025%. But there have been no reports from Japan with a large enough number of patients for statistical analysis.

In this paper, we report the prevalence of myasthenia gravis in a large group of patients with Graves' disease in Japan, and analyze the clinical findings in patients with myasthenia gravis and Graves' disease.

PATIENTS AND METHODS

There were 22,956 patients with Graves' disease who came to the Ito Hospital, Tokyo, during 1968-1979; 18,508 were female and 4,448 were male. Myasthenia gravis was diagnosed by history, physical examination, and response to edrophonium chloride. The diagnosis of Graves' disease was established by clinical findings and serum levels of thyroxine, triiodothyronine, and 24-hr 131I-thyroidal uptake.

RESULTS

The prevalence of myasthenia gravis in Graves' disease was 0.14% (33 out of 22,956 patients). Of the 33 myasthenia patients, 24 were female (0.13%) and 9 were male (0.20%); the male-to-female ratio was 1 to 2.6.

Age at onset of the myasthenia gravis patients was 2-48 years, and the average age at onset was 24.4. Fig. 1 shows the age at onset of myasthenia gravis patients with and without Graves' disease. The upper figure shows age at onset of myasthenia...
Myasthenia Gravis in Graves' Disease

Fig. 1. Age at onset of myasthenia gravis in patients with and without Graves' disease
The upper figure shows age at onset of myasthenia gravis in patients without Graves' disease, as reported by the Ministry of Public Welfare of Japan in 1979. The lower figure shows the age at onset of myasthenia gravis in patients with Graves' disease.

Fig. 2. Age at onset of Graves' disease in patients with and without myasthenia gravis
The upper figure shows age at onset of Graves' disease in patients without myasthenia gravis who came to the Ito Hospital in 1979. The lower figure shows age at onset of Graves' disease in patients with myasthenia gravis.

Gravis in patients without Graves' disease, as reported by the Ministry of Public Welfare of Japan in 1979. The lower figure shows the age at onset of our 33 cases with Graves' disease. The distribution of age at onset of myasthenia gravis in patients with Graves' disease is similar to that of patients without Graves' disease, and the peaks of age at onset in female are in the third decade in both. The high incidence of age at onset in male is in younger age, but no case of myasthenia gravis in patients with Graves' disease has onset before age 10. Fig. 2 shows age at onset of Graves' disease. The upper figure shows the distribution in the 1,658 new patients without myasthenia gravis who came to the Ito Hospital in 1979. The lower figure shows the results of the patients with myasthenia gravis. While the peak for age at onset of Graves' disease in patients without myasthenia gravis is at 25-35 years, that in patients with myasthenia gravis is about ten years lower. In patients with both Graves' disease and myasthenia gravis, the relationship between the onsets of the two diseases (Fig. 3) was investigated. The arrow shows the onset of Graves' disease. The column

Jpn J Med Vol 26, No 1 (February 1987)
Fig. 3. Relationship between the time of onset of the two diseases in patients with both Graves' disease and myasthenia gravis. The arrow shows the onset of Graves' disease. The number in parentheses show the number of patients.

According to Ossermann's classification of myasthenia gravis, 26 of our cases were Type I (ocular type) and 7 cases were Type II. There were no cases with the severe systemic form. Thymoma was not found by chest X-ray in any of the patients.

We compared the positive incidence of thyroid auto-antibodies, the size of the goiter, and the degree of exophthalmos between Graves' patients with and without myasthenia gravis (Table 1). The thyroid auto-antibodies were measured using commercial kits (thyroid test, TGHA, and Micromsome test, MCHA, from the Fujizaki Co., Ltd., Tokyo). The positive incidence of TGHA in Graves' patients with myasthenia gravis was not significantly different from that in those without. There was also no significant difference in the positive incidence of MCHA between Graves' patients with and without myasthenia gravis. Similar results were obtained for the degree of exophthalmos. The percentage of patients with large goiters was higher in Graves' patients with myasthenia gravis.

Serum T3U levels before treatment were 51.5 ± 10.5%; mean ± SD, n=11 with range from 31 to 79%, and those were not significantly different from values of uncomplicated Graves' patient (unpublished data).

The treatment of Graves' disease in patients with both diseases was as follows: 16 patients were treated with antithyroid drugs, 8 with radioiodine, and 9 by subtotal thyroidectomy. There were no patients whose myasthenia gravis was worsened with any method of treatment. Fig. 4 shows the relationship between thyroid function and the dose of an anticholinergic drug required to control the symptoms of myasthenia gravis. In 10 patients, the dose of anticholinergic drug could be decreased or terminated when the thyroid function was normalized. In one case treated with radioiodine, a higher dose of anticholinergic drug was required during transient hypothyroidism. No cases showed the "see-saw phenomenon."

DISCUSSION

There have been two reports on the prevalence of myasthenia gravis in patients with Graves' disease in Japan, which gave rates of 0.68% and 12.9%. The earlier one, by Shizume 5), analyzed 876 patients with Graves' disease. The second, with 77 patients with Graves' disease, was by Satoyoshi and Saku 6); the high incidence they report is due to the specialization of their hospital. We report here that the incidence of myasthenia gravis in Graves' disease in Japan is 0.14%, using a large number of patients. This incidence is not significantly different from the incidence in Europe (Table 2).

Concerning the relationship of onset of the two diseases, while the age at onset of Graves' disease in patients with myasthenia gravis was
Myasthenia Gravis in Graves' Disease

Table 1. Comparison of thyroid autoantibody, goiter size, and exophthalmos between Graves' patients with and without myasthenia gravis (MG)

<table>
<thead>
<tr>
<th></th>
<th>TGHA: + (%)</th>
<th>MCHA: + (%)</th>
<th>size of goiter* (%)</th>
<th>degree of exophthalmos</th>
</tr>
</thead>
<tbody>
<tr>
<td>with MG (n=33)</td>
<td>42.8</td>
<td>76.9</td>
<td>3.0</td>
<td>1.0</td>
</tr>
<tr>
<td>without MG (n=1658)</td>
<td>36.2</td>
<td>85.9</td>
<td>5.5</td>
<td>15.0 ± 2.88</td>
</tr>
</tbody>
</table>

*Size of goiter was estimated by palpation by the classification of Hichijo.

a, p < 0.05
b, mean ± S.D.

Fig. 4. Relationship between thyroid function and doses of anticholinergic drug required to control symptoms in patients with Graves' disease and myasthenia gravis

Clinical manifestations of Graves' disease in myasthenia gravis complicated cases were compared with those in myasthenia gravis uncomplicated cases. While goiter size was greater in myasthenia gravis complicated cases there were no significant differences in other immunological marker such as antithyroglobulin antibody, antimicrosomal antibody and the degree of exophthalmos. It has been reported that a “see-saw phenomenon” sometimes occurs during the treatment of hyperthyroidism. Although we analyzed the course of myasthenia gravis during the treatment of hyperthyroidism in 33 patients with both diseases, we could not find cases of such a phenomenon. In one case, the dosage of the anticholinergic drug required to control the symptoms of myasthenia gravis was higher during transient hypothyroidism, as has been reported by Gaelen and Levin. In papers reporting the see-saw phenomenon, patients in whom hypothyroidism developed during treatment may have been included. It is very important
to maintain the euthyroid state, especially in patients with both myasthenia gravis and Graves' disease.

REFERENCES


