Treatment of Myasthenia Gravis: A Comparison of the Natural Course and Current Therapies

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Ninety-five patients with generalized myasthenia gravis were followed for 10 years to evaluate the long term effects of prednisolone, thymectomy, or both, and they were compared with a group only with anticholinesterase treatment. Only 15.0% of the patients with anticholinesterase alone had showed improvement 10 years after the onset, but more than 60% of those treated with prednisolone, thymectomy, or both showed improvement. Especially thymectomy induced complete remissions at 10 years after surgery in more than 20% of the patients. There was no difference between the histology of the thymi and clinical severity, or anti-acetylcholine receptor (AChR) antibody titer. In patients who showed improvement classified “good” of higher 10 years after thymectomy with or without prednisolone, anti-AChR antibody titers swiftly decreased to 37.8% of the value before surgery, and remained low thereafter. This result suggests that the marked decrease in anti-AChR antibody titers within 1 month after thymectomy is a favorable prognostic sign in myasthenia gravis patients who have undergone thymectomy. ——— myasthenia gravis; prognosis; anti-AChR antibodies; thymectomy; prednisolone

Myasthenia gravis (MG) is a neuromuscular transmission disorder characterized by weakness and fatigue of the voluntary muscle. The antiacetylcholine receptor (AChR) antibody is considered to have a crucial role in defective neuromuscular transmission in myasthenia gravis patients, but no definitive correlation has been shown between the severity of the disease and anti-AChR titer. Various therapies have been used to treat myasthenia gravis. An anti-

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cholinesterase compound (physostigmine) was first used in 1934 for the diagnosis and management of MG (Walker 1934). In 1966 the effect of large doses of ACTH on severe MG was reported (von Reis et al. 1966). Later the beneficial effect of prednisolone (100 mg on alternate days) was reported (Warmolts et al. 1970). The efficacies of prednisolone and other immunosuppressive agents have been also shown (Seybold and Drachman 1974; Rowland 1980). Thymectomy, first used in 1939, has been modified extensively, and extended total thymectomy is currently recommended (Blalock et al. 1939; Masaoka and Monden 1981; Spath et al. 1987). The benefits of these therapies, in particular, of thymectomy and alternate-day prednisolone treatment, have been well documented and provide a rational approach to the management of most MG patients. Controversy, however, exists (Rowland 1980).

We evaluated the long term effects of prednisolone, thymectomy, and the combination of both treatments, and compared them with the effects of anticholinesterase alone and the changes in anti-AChR antibody titers during the treatment.

**SUBJECTS AND METHODS**

During the period of 1965–1990 we treated 212 myasthenia gravis patients in our hospital using anticholinesterase agents, corticosteroids, thymectomy, plasmapheresis and various combinations of these therapies. To evaluate the long term effects of these thera-

<table>
<thead>
<tr>
<th>Class</th>
<th>Daily disability</th>
<th>Respiratory assistance</th>
<th>Response to anticholinesterase</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>-</td>
<td>Unnecessary</td>
</tr>
<tr>
<td>1</td>
<td>Minor</td>
<td>-</td>
<td>Excellent</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
<td>-</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>-</td>
<td>Some</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
<td>-</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>Bedrest</td>
<td>+</td>
<td>None</td>
</tr>
</tbody>
</table>

2) Evaluation of clinical improvement (compared to pretreatment)

- Remission: all classes to 0
- Excellent: 3 ranks up
- Good: 2 ranks up
- Fair: 1 rank up
- Stable: no rank up
- Death
Treatment of Myasthenia Gravis

apeutic measures, we selected 95 patients with generalized MG whose clinical courses have been followed for more than 10 years. Diagnosis of MG was made on the basis of clinical signs and symptoms, measurement of anti-AChR antibodies, a positive response to edrophonium-chloride, results of the repetitive stimulation test, as well as histochemical or immunohistochemical (or both) studies of the motor endplate which had been made for 82 of the 95 patients. We separated these patients into 4 groups. Group 1 consisted of those treated only with anticholinesterase agents or with no drugs (natural course). Group 2 consisted of patients treated solely with prednisolone. Group 3 consisted of subjects who had had trans-sternal extended thymectomy but who had been given no prednisolone. Group 4 consisted of those patients who had undergone thymectomy and been prescribed prednisolone. The severity of the disease was rated according to modified Ossermann’s classification of 6 categories (Rowland 1980). The evaluations are shown in Table 1 (Oosterhuis et al. 1983).

Anti-AChR antibodies in the patients’ sera were measured by the radioimmuno-precipitation method described by Lindstrom with human skeletal muscle AChR as the antigen (Lindstrom et al. 1976). Because of the wide range of serum antibody titers, we have expressed titer values as the ratios of values after thymectomy, prednisolone administration, or both, to those before the treatment.

The paired t-test and Wilcoxon signed rank test were used for the statistical analysis of the differences in results.

Results

Group 1 (Fig. 1) consisted of 40 patients (12 men and 28 women, age range 15-61, mean age 38.0±1.9, mean severity score 1.63±0.02). Most had been treated before 1975, and thus had not had prednisolone or thymectomy. Although the initial MG condition had been mild, 34 (85.0%) showed no improvement 10 years after the onset; 11 remained unchanged, 15 had become worse and 8 (20.0%) had died (3 of invasive malignant thymoma). Only 2 (5.0%), whose initial severities were rated 1 had considerable responses to anticholinesterase agents and showed

![Fig. 1. Courses for group 1 (40 MG patients) followed for 10 years.](image-url)
remission. One of these subjects became worse 17 years post onset.

Group 2 consisted of 10 patients (2 men and 8 women, age range 15–70, mean age 35.9±4.6, mean severity score 2.28±0.11) who were treated with anti-cholinesterase agents and prednisolone (Fig. 2). Thymectomy was not performed because of the risk of using anesthesia or the patient’s rejection of surgery. We used alternate-day prednisolone therapy (the initial dosage was 30–60 mg/alternate day) and gradually tapered off the dose. At 10 years, 6 (60%) had improved and their anti-AChR antibody titers had decreased significantly (51.7±19.6% of the pretreatment values, p <0.01). None had experienced life-threatening side effects such as hemorrhagic gastric ulcer or hyperglycemia.

Group 3 consisted of 20 patients (7 men and 13 women, age range 22–59, mean...
age 34.4 ± 2.75, mean severity score 1.78 ± 0.01), none of whom received prednisolone after thymectomy (Fig. 3 left). Ten years after surgery, 13 (65%) had improved. This number included 6 remission cases.

Group 4 consisted of 25 patients (6 men and 19 women, age range 27–68, mean age 40.9 ± 2.75, mean severity score 2.14 ± 0.04), all of whom received prednisolone after thymectomy (Fig. 3 right). In general, prednisolone was started when the patient reached the stable stage, usually 1 month after surgery. The initial alternate day dose was 40–60 mg, which was gradually tapered off. Fifteen of this group (60%) showed improvement and included 4 remission cases. Four (16%) died of invasive malignant thymoma, but there was no death caused by a myasthenic crisis. Seven (28%) were still receiving prednisolone 10 years after thymectomy because of insufficient improvement or exacerbation when the medication was discontinued. The mean prednisolone administration period was 4.8 years. Because the patients who did not show satisfactory improvement were usually treated with prednisolone, the severity for group 3 differs from group 4. The severity scores at thymectomy for these groups were 1.78 ± 0.01 and 2.14 ± 0.04 (p < 0.01), respectively.

When group 3 and 4 were combined (13 men and 32 women, age range 22–68, mean age 38.6 ± 1.6), 28 (62.2%) of the 45 patients, who had undergone thymectomy showed improvement (Fig. 4). Fifteen patients who showed improvement rated at “good” or higher improvement 10 years after thymectomy individually listed (Table 2); 12 (80%) showed remarkable improvement within 1 year, with anti-AChR antibody having significantly decreased to 37.8 ± 5.4% of the value prior to thymectomy (p < 0.01) 1 month postsurgery, at 3 months to 31.2 ± 3.9% (p < 0.01), and at 6 months to 26.1 ± 7.2% (p < 0.01) (Fig 5).

The duration of the disease before thymectomy and clinical improvement are

![Fig. 4. Courses for 45 thymectomized MG patients (groups 3 and 4).](image-url)
Table 2. Patients who classified “good” or higher improvement 10 years after thymectomy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Initial class</th>
<th>Duration noted (years)</th>
<th>Pathology</th>
<th>Steroid</th>
<th>AChR at 1 M</th>
<th>Improved after</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>32</td>
<td>3</td>
<td>6.5</td>
<td>N</td>
<td>-</td>
<td>85.2%</td>
<td>1 year</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>33</td>
<td>2</td>
<td>7.0</td>
<td>N</td>
<td>-</td>
<td>35.2</td>
<td>4 years</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>34</td>
<td>1</td>
<td>0.6</td>
<td>N</td>
<td>-</td>
<td>24.9</td>
<td>3 years</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>29</td>
<td>2</td>
<td>4.3</td>
<td>Hp</td>
<td>-</td>
<td>36.2</td>
<td>3 months</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>22</td>
<td>2</td>
<td>2.1</td>
<td>Hp</td>
<td>-</td>
<td>0</td>
<td>3 months</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>42</td>
<td>1</td>
<td>2.0</td>
<td>Hp</td>
<td>-</td>
<td>33.2</td>
<td>6 months</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>31</td>
<td>1</td>
<td>3.4</td>
<td>Hp</td>
<td>-</td>
<td>18.2</td>
<td>6 months</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>42</td>
<td>3</td>
<td>0.8</td>
<td>N</td>
<td>+</td>
<td>36.4</td>
<td>1 year</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>42</td>
<td>3</td>
<td>15.0</td>
<td>N</td>
<td>+</td>
<td>29.3</td>
<td>6 months</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>40</td>
<td>3</td>
<td>0.5</td>
<td>Hp</td>
<td>+</td>
<td>72.0</td>
<td>1 year</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>40</td>
<td>3</td>
<td>0.7</td>
<td>Tm</td>
<td>+</td>
<td>29.7</td>
<td>1 year</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>51</td>
<td>3</td>
<td>1.4</td>
<td>Tm</td>
<td>+</td>
<td>58.3</td>
<td>4 years</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>51</td>
<td>1</td>
<td>4.0</td>
<td>Tm</td>
<td>+</td>
<td>42.4</td>
<td>3 months</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>27</td>
<td>1</td>
<td>0.7</td>
<td>Tm</td>
<td>+</td>
<td>29.4</td>
<td>3 months</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>48</td>
<td>1</td>
<td>0.8</td>
<td>Mal</td>
<td>+</td>
<td>36.2</td>
<td>1 year</td>
</tr>
</tbody>
</table>

N, normal thymus or fatty tissue; Hp, hyperplasia; Tm, thymoma; Mal, malignant thymoma.

Fig. 5. Changes in anti-AChR antibodies after thymectomy; 45 MG thymectomy patients and 15 of whom had good prognoses (see Table 2).

□, Tx: 45 patients; ○, remission + good improvement; ■, prednisolone (-); ▲, prednisolone (+). *p < 0.05; **p < 0.01.
Fig. 6. Effect of the period between MG onset and thymectomy on clinical features of patients 10 years after surgery.

Fig. 7. Effect of thymic pathology on clinical features and ratios of anti-AChR antibodies 10 years after thymectomy.

shown in Fig. 6. Thymectomy within 1 year after the onset gave the highest percentage of remission (5 of 10 patients, 50%) 10 years after surgery, though patients in all categories showed improvement.

Histological features at surgery were shown in Fig. 7: Normal thymus or fatty tissue were found in 15 patients; hyperplasia in 15 patients; thymoma in 11 patients; and malignant thymoma in 4 patients. There was no difference between the histology of the thymi at surgery and clinical severity, or anti-AChR antibody titer. Ten years after surgery there was no relationship between clinical improvement and the histology of the thymi, but anti-AChR antibody titers of patients with hyperplasia showed a significant decrease (48.9 ± 20.5%, p < 0.05).
DISCUSSION

Various therapies have been used to treat MG; anticholinesterase agents, corticosteroids, immunosuppressive agents, plasmapheresis and thymectomy. Any randomized controlled study in which patients with myasthenia gravis are randomly allocated to surgery, medical therapy alone, or combined therapy has not been performed (Rowland 1980, 1987). Therefore an opinion can be hardly expressed on relative effectiveness of the therapies.

We classified patients who had been treated only with anticholinesterase agents or with no drugs, in the "natural" course group (group 1) and compared the results of other treatments. The administration of prednisolone (group 2), thymectomy (group 3), or both (group 4), significantly increased the percentage of patients who showed improvement or remission. The percentages of patients who showed improvement at 10 years were not different among the group 2, 3 and 4, though no patients showed remission in group 2. Although our results provide no definite evidence that thymectomy superiors the prednisolone alone at the end of following period, they are consistent with the current belief that the use of both corticosteroids and thymectomy produces a significant improvement or remission for MG patients (Mann et al. 1976; Bolooki and Schwartzman 1978; Johns 1987).

Although, there have been no controlled trials nor long term follow-up studies, most neurologists advocate thymectomy for all adults with generalized MG regardless of the existence of thymoma. Thymectomy has been reported to provide improvement or remission in 66 to 90% of MG patients. The ability to perform safer thymectomies, the availability of safer anesthesias, intensive-care monitoring, and the use of better surgical techniques may have contributed to the better results in recent years, thereby enhancing the choice of thymectomy. Considerable controversy still exists, however, as to whether, when, and how thymectomy should be performed. As regards thymic histology, 40 to 80% of MG patients are reported to show thymic hyperplasia; but, the effect of thymectomy on the patient with thymic hyperplasia has not yet been determined (Genkins et al. 1975; Mulder et al. 1989). Despite varying opinions, the efficacy of thymectomy has been reported for patients with juvenile MG (those under the age of 20); for patients who, at the time of surgery, have had MG for less than 5 years; and for patients who have had no prior anticholinesterase medication (Rowland 1980; Rubin et al. 1981).

In our study, the long term beneficial effect of thymectomy was observed in patients with all types of thymic histology, except malignant thymoma, and in patients who had thymectomies within 1 year of the onset of MG. These results are consistent with those of previous reports (Seybold et al. 1978; Rubin et al. 1981).

Recently, thymectomy followed by large doses of prednisolone has been recommended (Genkins et al. 1975; Mulder et al. 1989). In our series patients
who underwent thymectomy followed by prednisolone treatment and those who underwent thymectomy alone showed similar percentages of improvement 10 years later, though the initial severity scores of the former were higher than those of the latter; the reason for this is that we usually started prednisolone treatment for patients who have some remained signs and symptoms at one month after surgery; therefore, the efficacies of these treatments could not be directly compared.

Serum anti-AChR antibody is present in 90% of patients with generalized MG, but there is no definite correlation between serum anti-AChR titer and the clinical severity of MG, probably because of the heterogeneity of anti-AChR. Serum anti-AChR levels are correlated with clinical changes in individual patients before and after plasma exchange (Newsom-Davis et al. 1978). Previous reports on the effects of thymectomy or prednisolone on serum anti-AChR antibody, however, gave conflicting results (Olanow et al. 1982; Vincent et al. 1983). Highly significant correlations between changes in clinical conditions and change in antibody levels after thymectomy have been reported; in particular, marked reductions in anti-AChR in patients who were in remission or showed marked improvement 1 year after surgery (Vincent et al 1983; Oosterhuis et al. 1985). As a whole there was a slight reduction in serum anti-AChR levels after thymectomy in our study; but, when we observe patients who showed marked improvement or remission 10 years after thymectomy, 80% had improved markedly 1 year after surgery and their anti-AChR levels had fallen to 37.8% of the pre-thymectomy value 1 month after surgery and remained low during the observational period. This marked decrease of anti-AChR by 1 month after surgery was associated with the improvement of clinical symptoms and signs in some patients, but not in all. We treated the patients who did not show significant improvement with prednisolone, which may have been responsible for their marked improvement or remission during the observational period. These results indicate that the marked decrease of anti-AChR 1 month after thymectomy was a favorable prognostic sign in myasthenia gravis patients who underwent thymectomy with or without subsequent prednisolone therapy. Thus we recommended prednisolone treatment for patients who still have myasthenic signs and symptoms or showed no marked reduction of anti-AChR antibodies at one month after thymectomy.

References


