Development of Generalized Disease at 2 Years in Patients With Ocular Myasthenia Gravis

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Background: Generalized myasthenia gravis will develop in more than 50% of patients who present with ocular myasthenia gravis, typically within 2 years. The optimal treatment of ocular myasthenia gravis, including the use of corticosteroids, remains controversial. In addition, the prevalence of thymoma and the optimal performance of the edrophonium chloride test for ocular myasthenia remain unknown.

Objective: To assess the effect of oral corticosteroid therapy on the frequency of development of generalized myasthenia gravis within 2 years, the incidence of thymoma, and the amount of edrophonium needed for a positive test result in patients with ocular myasthenia gravis.

Methods: We reviewed an ocular myasthenia gravis database of 147 patients. Patients underwent measurement of acetylcholine receptor (AChR) antibody levels and chest computed tomography. Unless contraindicated, patients with diplopia were recommended for therapy with prednisone, up to 40 to 60 mg/d, with the dosage tapered for 5 to 6 weeks. Most continued to receive daily or alternate-day doses of 2.5 to 10 mg to prevent diplopia. Patients not given prednisone (untreated group) received pyridostigmine bromide or no medication. After the diagnosis, we documented the signs and symptoms of ocular and generalized myasthenia gravis and performed 2-year follow-up in 94 patients.

Results: The mean dose of edrophonium chloride to give a positive response was 3.3 mg (SD, 1.6 mg) for ptosis and 2.6 mg (SD, 1.1 mg) for ocular motor dysfunction. Thymoma occurred in 1 patient (0.7%). Generalized myasthenia gravis developed within 2 years in 4 of 58 treated and 13 of 36 untreated patients. The odds ratio (OR) for development of generalized disease in the treated group was 0.13 (95% confidence interval [CI], 0.04-0.45) compared with the untreated group. The AChR antibody level was not predictive of development of generalized myasthenia gravis at 2 years, but the risk was greater in patients with abnormal AChR antibody levels (OR, 6.33; 95% CI, 1.71-23.42). Logistic regression that included age, abnormal AChR antibody level, and prednisone therapy yielded significance only for abnormal AChR antibody level (OR, 7.03; 95% CI, 1.35-36.64) and treatment (OR, 0.06; 95% CI, 0.01-0.30).

Conclusions: At 2 years, prednisone treatment appears to reduce the incidence of generalized myasthenia gravis to 7% in contrast to 36% of patients who did not receive prednisone. Thymoma, although uncommon, occurs in ocular myasthenia gravis. Only small amounts of edrophonium are needed to diagnose ocular myasthenia gravis.

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duce the frequency of deterioration of ocular myasthenia gravis to the generalized form of the disease, the obvious benefits would include prevention of debilitating disease, long-term immunosuppressive therapies, and hospitalizations. If larger dosages are used for a short time, few major adverse effects should result, even if lower doses are continued for many months. Kupersmith et al reported that a moderate dose, reduced during a 6-week course and followed by low-dose daily or alternate-day corticosteroid therapy, reduced the conversion rate to generalized myasthenia gravis to 9% in a small cohort of 32 patients. The development of systemic hypertension, diabetes mellitus, osteoporosis, gastrointestinal tract disorders, or infectious illness that typically occur with moderate-to-high-dose daily or alternate-day therapy should be minimized with long-term dosages of no greater than 10 mg/d, use of corticosteroids to control blood pressure and hyperglycemia, and use of prophylactic interventions for gastrointestinal tract and bone dysfunction. The purpose of this study was to determine whether the frequency of development of generalized myasthenia gravis at 2 years in patients presenting with the ocular form of the disease could be reduced by treatment with low-dose corticosteroid therapy after a moderate-dose regimen, tapered during a 6-week course.

**METHODS**

**DESIGN**

We evaluated the medical charts of patients with ocular myasthenia gravis at the Neuro-ophthalmology Service at New York Eye and Ear Infirmary (1984-2000), New York University School of Medicine (1984-1997), and the Institute of Neurology and Neurosurgery of Beth Israel Medical Center, New York (1997-2000). We extracted the data to fill in an ocular myasthenia gravis database created in 1997. All new and old patients with ocular myasthenia gravis who came to the clinics from 1997 forward had their medical chart data maintained in a systematic matter, and all were informed of the intention to keep their data in an organized confidential database to try to answer the questions of this study. Inclusion criteria consisted of being 2 years or older at the first neuro-ophthalmologic examination and having clinically evident ocular myasthenia gravis and no subjective symptoms or clinical findings suggestive of generalized myasthenia gravis (any muscle weakness below the neck or in the facial muscles except the orbicularis oculi). We used the following criteria for diagnosis of ocular myasthenia gravis:

1. Ptosis in one or both upper lids not due to local eyelid disease, preferably that could fatigue or recover with rest.
2. Extraocular muscle weakness in one or both eyes, not in a strict third nerve muscle innervation pattern; if the weakness was in the lateral rectus only, clear-cut fatigability, recovery, or a positive edrophonium chloride test results.
3. Weakness that could be present in one or both orbicularis oculi but no other weakness of the muscles of the head and neck.
4. No pupillary abnormality other that from previous local disease or surgery.
5. Fatigue of the affected muscle with clear-cut worsening of the ptosis after upward gaze for 30 to 60 seconds or worsening of the monocular duction after 120 seconds of gaze in the direction of action; recovery of the upper-eyelid ptosis to almost normal after 30 seconds to 10 minutes of eyelid closure, and recovery of the monocular duction after 120 to 180 seconds of gaze in the direction of the antagonist muscle, or a positive edrophonium chloride test result.

Patients with ocular myasthenia gravis beginning before age 2 years were excluded. Patients with signs of restrictive myopathy of abduction or supraduction due to dysthyroid ophthalmopathy were excluded. Patients with dysthyroid ophthalmopathy who developed exotropia and a positive edrophonium test were included. All patients had definite worsening of lid or ocular motor dysfunction with prolonged use of the involved muscle and recovery with rest, demonstrable on the clinical examination, or positive results of an edrophonium test. In questionable cases, patients had to have abnormal findings on repetitive stimulation electromyography with a minimum decrement of 10%.

The edrophonium test was performed as previously described. After baseline, measurements, including determination of ocular misalignment in primary gaze by means of the prism alternate cover test, were established for the abnormal function(s) to reverse, no more than 1 to 2 mg were injected during a 30-second period, with a cumulative total of 10 mg if necessary. During the 30-second interval after each dose, only definite improvement in the ptosis or ophthalmoparesis was documented, and the prism alternate cover test was performed in the primary gaze and in the affected field of gaze. The infusion was aborted when a clear positive response occurred. The number of milligrams required to reach the end point was documented.

All patients underwent contrast-enhanced computed tomography (CT) of the chest to look for the presence of a thyroid. The serum was tested for fasting blood glucose and AChR-binding antibody levels (performed in several different commercial laboratories). Patients underwent blood studies for thyroid dysfunction unless they were already known to have a history of hypothyroidism or hyperthyroidism.

Patients were not randomized for therapy. Because previous work suggested that corticosteroids alleviate diplopia in the primary gaze, except in patients who refused or had contraindications, patients with diplopia in primary or downward gaze and extraocular muscle dysfunction or ptosis that blocked vision and was unresponsive to pyridostigmine bromide were treated with prednisone (treated group). Patients with these exceptions, including active gastrointestinal tract ulcer or a history of tuberculosis, diabetes mellitus that was difficult to control, severe hypertension, and congestive heart failure, and patients who refused treatment, constituted the untreated group. The duration of symptoms before starting treatment was not uniform. Patients with a history of a positive purified protein derivative finding or 1 or more calcified lesions suggestive of healed tuberculosis on the chest CT received somiai, 300 mg/d, and pyridoxine hydrochloride, 50 mg/d, concomitantly with the prednisone.

All prednisone-treated patients were prescribed a daily histamine blocker (ranitidine hydrochloride, nizatidine, or famotidine hydrochloride) and supplemental calcium, 1000 to 1500 mg/d, as long as prednisone therapy was continued. The prednisone dosage was started at 10 mg/d for 2 days, followed by 20 mg/d for 2 days. The dosage was increased to 30 mg/d or more for 4 to 5 days. The dosage was reduced to 10 mg/d at 1 week, followed by 30 mg/d for 1 week, 20 mg/d for 4 weeks, 10 and 20 mg/d alternated for 1 week, and then 10 mg/d. The dosage was further reduced by 2.5 mg each week while clinically titrating the dosage to the patient’s clinical symptoms and findings of ocular myasthenia gravis. Most patients in the prednisone treatment group continued to receive a daily or alternate daily dose of 2.5 to 10 mg. Patients not treated with prednisone received pyridostigmine as necessary and tolerated to relieve ptosis. Few patients continued to receive pyridostigmine to alleviate diplopia because this drug failed to accomplish this goal.

All the patients were questioned and examined at each evaluation by one of us (M.J.K.) for the presence of general-
ized myasthenia gravis and any corticosteroid complications during the previous period. At each visit, patients underwent probing for symptoms of fatigue, change in activity due to fatigue or weakness, shortness of breath, change in voice, problems swallowing, or weakness in daily activities and/or exercise. The strength of facial, jaw, and neck flexion and extension and the extremities, with particular attention to the proximal muscle groups, were evaluated at each visit. Baseline and follow-up bone density studies were not routinely performed. A neuromuscular specialist performed an evaluation for each patient with symptoms of signs of generalized myasthenia gravis for corroboration.

DATA ANALYSIS

Our primary goal was to determine the incidence in the treated and untreated groups of development of generalized myasthenia gravis within 2 years and to determine potential risk factors. Baseline factors, including gender, age, AChR antibody level, whether the AChR antibody level was abnormal, and whether patients were 50 years or older, were compared between the 2 treatment groups using the 2-tailed t test. The odds ratio (OR) for development of generalized myasthenia gravis within 2 years for each factor or treatment group was expressed with 95% confidence intervals (CIs). Logistic regression was used to determine whether the AChR antibody level or age was significantly associated with the development of generalized myasthenia gravis at 2 years. Multivariate logistic regression was also used to test the strength of the association with generalized myasthenia gravis at 2 years, controlling for other risk factors. Kaplan-Meier estimation was used to analyze the effects of treatment and abnormal AChR levels on the development of generalized myasthenia gravis during the entire study period. A log-rank statistic was used to test for group differences in the Kaplan-Meier estimates. A univariate proportional hazards regression model was used to evaluate the association of age with the development of generalized myasthenia gravis during the entire study period. Proportional hazards regression was also used to estimate a multivariate model for time to development of generalized myasthenia gravis in the entire study period. All statistical comparisons were performed using a level of significance of \( P < 0.05 \).

As a secondary goal of this study, we report the incidence of thymoma and the dosage of edrophonium needed to induce a positive effect on lid and extraocular muscle dysfunction.

RESULTS

We included 147 patients who met our criteria for ocular myasthenia gravis in our database. These included 84 male and 63 female patients, with a mean age of 50 years (SD, 21 years; range, 2-80 years) and a mean follow-up of 3.6 years (SD, 3.2 years; range, 0.5-16.0 years). Six patients were 10 years or younger. The diagnosis was established by means of the fatigue/recov-ery method in 67 patients and a positive edrophonium test result in 80 of 83 patients. The 3 patients who had a negative edropho-nium test result had definitive fatigue and recovery phenomena on the clinical examination and abnormal re-petitive nerve stimulation electromyography results. The mean dose of edrophonium chloride to give a positive response for ptosis was 3.3 mg (SD, 1.6 mg) and for extraocular muscle weakness was 2.6 mg (SD, 1.1 mg). A cumulative dose of greater than 4 mg was needed to demonstrate a positive response for the ptosis in 2 patients (6 and 7 mg) and for extraocular muscle function in 2 patients (6 and 7 mg), one of whom required 7 mg for reversal of ptosis and ocular movement limitation. One of these 3 patients required the 7-mg dose to reverse the lid and extraocular muscle dysfunction. The AChR antibody level was abnormal in 35% of patients. The mean level was 4.0 nmol/L (SD, 13.3 nmol/L). Thymoma was diagnosed by means of CT in 3 patients. Two of these patients underwent surgical excision of the mediastinal mass; thymoma was found in one and thymic hyperplasia in the other. The third patient refused surgery and underwent a 14-year follow-up with no change in the mediastinal mass; thus, thymoma occurred in only 1 case (0.7% of patients with ocular myasthenia gravis).

The 2-year follow-up was accomplished in 94 patients, 58 of whom received prednisone. Forty-five patients were 50 years or older. For patients in whom generalized myasthenia gravis did not develop within 2 years, the mean duration of follow-up was 4.6 years (SD, 3.0 years; range, 2-16 years). Except for the ocular motor dysfunction, no significant differences were found between the treated and untreated groups in terms of background characteristics (Table 1).

Table 2 compares the rate of development of generalized myasthenia gravis within 2 years in the treated and untreated groups along with several background factors. Generalized myasthenia gravis developed within 2 years in 4 (7%) of 58 treated and in 13 (36%) of 36 untreated patients. For the treated group, the OR for development of generalized disease was 0.34 (95% CI, 0.14-0.80) compared with the untreated group. Fifteen of the 17 patients in whom generalized myasthenia gravis developed within 2 years had the generalized form within the first half of the first year. Gender and age of at least 50 years were not significant risk factors for development of generalized myasthenia gravis. However, actual age demonstrated a significant association with generalized myasthenia gravis within 2 years (\( P = .02 \)). Female patients younger than 40 years may have less risk for development of generalized disease. In only 1 (7%) of 13 female patients younger than 40 years (7 treated with prednisone), in contrast to 7 (32%) of 22 who were 40 years or older (14 treated with prednisone), generalized myasthenia developed at 2 years. Generalized disease developed at 2 years in 3 (14%) of the 22 male patients younger than 40 years (14 treated with prednisone) and 6 (17%) of those 40 years or older (22 treated with prednisone).

The level of AChR antibody was not a significant predictor of development of generalized myasthenia gravis at 2 years (\( P = .87 \)), although the risk for development of

Table 1. Baseline Features of Patients With OMG

<table>
<thead>
<tr>
<th>Group</th>
<th>Treated</th>
<th>Untreated</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, No. F/M</td>
<td>21/37</td>
<td>16/20</td>
<td>. . .</td>
</tr>
<tr>
<td>Mean (SD) age, y</td>
<td>49.2 (18.9)</td>
<td>46.0 (23.9)</td>
<td>.50</td>
</tr>
<tr>
<td>Diplopia, No. of patients</td>
<td>51</td>
<td>25</td>
<td>.03</td>
</tr>
<tr>
<td>Abnormal AChR antibody level, %</td>
<td>31</td>
<td>39</td>
<td>.51</td>
</tr>
<tr>
<td>Mean AChR antibody level, nmol/L</td>
<td>5.9 (19.1)</td>
<td>2.3 (3.7)</td>
<td>.37</td>
</tr>
<tr>
<td>Range</td>
<td>0-116</td>
<td>0.12-12</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: AChR, acetylcholine receptor.
generalized myasthenia gravis was greater in those patients with abnormal AChR antibody levels than in those with normal levels or negative findings (OR, 6.33 [95% CI, 1.71-23.42]). A logistic regression that included actual age, abnormal AChR antibody level, and prednisone treatment yielded significance only for abnormal AChR antibody level (OR, 7.03 [95% CI, 1.35-36.64]) and prednisone treatment (OR, 0.06 [95% CI, 0.01-0.30]). The effect of age was not significant after controlling for abnormal AChR antibody level and treatment (P = .31).

Generalized myasthenia gravis developed in 24 patients during the entire follow-up period, including 9 (16%) in the treated group and 15 (42%) in the untreated group. The Figure shows the Kaplan-Meier estimate comparing the 2 groups. The log-rank statistic indicated that there was a significant difference in the rate of development of generalized myasthenia gravis in the entire study period (P = .003). During the entire study period, generalized myasthenia gravis occurred in 12 (48%) of 25 patients with abnormal levels of baseline AChR antibody compared with 7 (14%) of 49 patients with a normal AChR antibody level. The log-rank statistic for the difference in generalized myasthenia gravis rates in the AChR antibody groups was also significant (P = .003). In addition, age showed a significant positive association with development of generalized myasthenia gravis in the entire study period (P = .03). Proportional hazards regression found that only abnormal AChR antibody level and prednisone treatment were significant (abnormal AChR antibody level: relative risk [RR], 4.55 [95% CI, 1.65-12.35]; prednisone treatment: RR, 0.15 [95% CI, 0.6-0.41]). Age was not significant in the multivariate model (P = .28). No corticosteroid-treated patient sustained a clinically apparent fracture of a vertebra or hip, osteonecrosis, new systemic hypertension, an infection requiring hospitalization, or a gastrointestinal tract ulcer. Hyperglycemia requiring a hypoglycemic agent or worsening of existing diabetes mellitus occurred in 10% of patients, none of whom required insulin.

Our results confirm those of previous reports that suggest that the edrophonium test should be administered using increments of 1 to 2 mg and immediate evaluation in patients with ocular myasthenia gravis.13-15 Using this technique resulted in a positive test result in 96% of patients undergoing testing. For ptosis and ocular muscle dysfunction, an average dose of less than 4 mg was needed for the diagnosis. Six or more milligrams were required in less than 4% of subjects, and as much as 10 mg still failed to yield a positive result in 3.6% of patients. These data support the suggestion that smaller interval and total doses are required to diagnose ocular myasthenia gravis compared with generalized myasthenia gravis.13,10

Only 1 patient (0.7%) of those with ocular myasthenia gravis had a thymoma found on CT and verified pathologically.

The risk for generalized myasthenia gravis at 2 years was increased in patients with an abnormal AChR antibody level, but the absolute level was not predictive. The absolute age correlated with the development of generalized disease, but patients 50 years or older did not appear to undergo conversion at a higher frequency. In general, gender was not a risk factor, except generalized myasthenia gravis developed less often within 2 years in women younger than 40 years.

The optimal therapy for ocular myasthenia gravis has not been determined, and the administration of corticosteroids to eliminate extraocular muscle limitation and diplopia has been controversial.20,21 Our entire population with ocular myasthenia gravis had a lower percentage of patients with abnormal AChR antibody levels. We suspect this is due to the inconsistencies of performing this assay in commercial laboratories. We do not be-
lieve that our findings reflect inclusion of patients with other diagnoses, since all the patients were followed up, with almost all undergoing reevaluation after at least 6 months, and most undergoing follow-up for 2 years or longer. In addition, some of these patients had progression of ocular myasthenia gravis findings and symptoms, whereas generalized myasthenia gravis developed in others. However, we acknowledge, as in all clinical diagnoses that are made without pathological confirmation, that misdiagnoses can occur. Results of the fatigue-and-rest and edrophonium tests are considered robust, but even these tests can give false-positive results.22

Our current case series of 94 patients supports the hypothesis that corticosteroid treatment that does not cause significant systemic complications in patients with ocular myasthenia gravis may significantly reduce the prevalence of generalized myasthenia gravis at 2 years.

Corticosteroids interfere with the inflammatory and immunological dysfunction that injures the AchR and the neuromuscular junction. Although large doses of corticosteroid can block neuromuscular transmission and cause weakness, corticosteroid therapy appears to increase AchR synthesis and augments the organization of the postsynaptic membrane.23-25 If corticosteroid suppression of the destructive process occurs before detectable muscle weakness, a significant number of postsynaptic AchRs may have been spared.

In vitro studies provide mechanisms that may explain the corticosteroid benefits that are not related to immunosuppression. Glucocorticoids increase the number of AchRs in culture of human muscle,26 and this increase can be seen after 6 days of dexamethasone treatment in a dose-related manner.27 Dexamethasone also seems to reduce the AchR loss in human muscle culture cells induced by the serum from patients with myasthenia gravis. In damaged neuromuscular junctions, the junctions increase in size after 4 weeks of hydrocortisone or dexamethasone exposure. In addition, the length and number of postsynaptic folds and depths of postsynaptic clefts increase after 3 weeks of hydrocortisone treatment.24

Immunomodulation and immunosuppression appear to reduce deterioration of ocular myasthenia gravis to generalized myasthenia gravis. In one study, thymectomy was performed in 18 patients. No generalized myasthenia gravis occurred in any subject at 2 years. However, patients were followed up for 6 months before surgery so that patients who deteriorated before 6 months were not included.27 Immunosuppression with azathioprine sodium, usually administered concomitantly with prednisolone, also significantly reduces (12% compared with 64% for those without immunosuppressive treatment) the development of generalized myasthenia gravis.28 In patients with all stages of myasthenia gravis, spontaneous remission can occur in 20% of untreated cases, although in almost all of these patients, the disease recurs.29 One study suggested that treating generalized myasthenia with corticosteroids early in the course seems to induce remission if administered before 1.4 years and is less likely to result in a remission if administered after 4.3 years.7

In a retrospective study of 248 patients with ocular myasthenia gravis for at least 1 month after the onset of symptoms, of the 66% who later developed generalized myasthenia gravis, generalized myasthenia gravis appeared within 6 months in 58% and within 1 year in 78%.30 It appears advantageous to prevent generalized myasthenia gravis during the first year, since in all previous reports the risk for development of generalized myasthenia gravis decreases when the duration of ocular myasthenia gravis exceeds 1 year and is even lower after 2 years. One of our patients, who required 5 mg of prednisone every 3 days to prevent severe ophthalmoplegia, stopped the therapy after 3 years, and generalized myasthenia gravis developed 4 years later. Whether early intervention with low dosages of corticosteroid therapy permanently and favorably alters the natural history of this disorder or whether generalized myasthenia gravis will eventually develop if corticosteroid therapy is stopped remains an open question.

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REFERENCES


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