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Thymectomy in the treatment of ocular myasthenia gravis

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Background: Thymectomy is an effective and accepted treatment for myasthenia gravis, but thymectomy for ocular myasthenia gravis (Osserman stage I) is controversial.

Objective: To assess the efficacy and propriety of thymectomy for the treatment of ocular myasthenia gravis.

Methods: We conducted a review and follow-up of all patients who had thymectomy for the treatment of ocular myasthenia gravis between 1970 and 1998 at the University of California, Davis, Medical Center, and the University of Rome, "La Sapienza," Rome, Italy. Patient response to thymectomy was categorized as follows: *cured,* patients who became symptom-free and required no further medication; *improved,* patients who required less medication and whose symptoms were less severe; *unchanged,* patients whose symptoms and medications were the same; *worse,* patients who had more severe symptoms, needed more medication, or died.

Results: Sixty-one patients (mean age 37 years; range 14–73 years) were followed up for a mean duration of 9 years (range 0.5–29 years). Ocular myasthenia gravis with mixed and cortical thymomas, stages I to IV, occurred in 12 patients, and ocular myasthenia without thymomas occurred in 49 patients. Transsternal thymectomy (n = 55) and transcervical thymectomy (n = 6) resulted in cure in 31 (51%) patients, improvement in 12 (20%) patients, no change in 16 (26%) patients, and worsening of symptoms (including 1 postoperative death) in 2 patients. Patient outcomes were statistically independent of the duration of preoperative symptoms (mean 9.5 months), patient age, or the presence or absence of thymoma. In patients with ocular myasthenia, 70% were cured or improved after thymectomy; in the subgroup of patients with ocular myasthenia and thymoma, 67% were cured or improved.

Conclusion: Thymectomy is an effective and safe treatment for patients with ocular myasthenia gravis.

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Thymectomy has a generally accepted beneficial role in the treatment of myasthenia gravis (MG), but controversy persists regarding the indications and timing for operations. Since thymectomy was first described in association with MG by Sauerbruch[1] in 1912 and for the treatment of MG by Blalock and associates[2] in 1939, therapeutic advances have included the use of anticholinesterase drugs, corticosteroids, and other immunosuppressive medications. These adjuncts to thymectomy, better diagnostic tools, and improved critical care support have progressively

TABLE 1. Distribution of stage, cell type, and clinical outcome of patients with ocular myasthenia gravis (MG) and thymoma

Patient (age [y], sex)	Duration of symptoms	Thymoma stage	Histology	Response of ocular MG	Cause of death	Years postop
1 (54, M)	1	III	Mixed	Cured	Recurrence	4
2 (35, M)	1	IV	Cortical	Cured	Recurrence	4
3 (25, M)	5	I	Cortical	Operative death	Bleeding	0
4 (27, F)	4	IV	Mixed	Improved	Recurrence	7
5 (48, M)	3	III	Cortical	Improved	Recurrence	5
6 (22, F)	1	I	Mixed	Stable	Alive	10
7 (36, F)	1	II	Cortical	Cured	Alive	6
8 (65, M)	4	II	Cortical	Improved	Alive	5
9 (40, M)	2	II	Cortical	Improved	Alive	5
10 (42, M)	24	I	Cortical	Cured	Myocardial infarction	1
11 (64, M)	8	II	Cortical	Stable	Alive	4
12 (61, F)	2	I	Cortical	Stable	Alive	4

TABLE 2. Summary of literature demonstrating lack of consensus for optimal treatment of ocular MG

Studies	Year	No. of patients	Conclusions
Schumm et al[7]	1985	18 with ocular MG	Surgery for patients who do not respond to medical therapy
Papatestas et al[8]	1987	2062 with MG[a] 962 had thymectomies, 12 with ocular MG	Advantage to thymectomy seen in all stages
Evoli et al[9]	1988	247 with MG, 24 with ocular MG	Thymectomy is not effective in patients with ocular MG
Hatton et al[10]	1989	11 with ocular MG	Results of surgical and nonoperative treatment are equal
Nakamura et al[13]	1996	22 with ocular MG	Clear benefit of surgery
Masaoka14	1996	375 with MG, 40 with ocular MG	Thymectomy is effective treatment for both MG and ocular MG

improved patient outcomes. However, these advances have also complicated defining the role of thymectomy. Prospective studies have been difficult to design and interpret because of the variability of medical treatment and the natural history of the disease itself.

A survey of neurologists with special interest in MG in 1990 showed that most of them believed thymectomy to be indicated in patients with thymomas and in selected cases of generalized MG. However, they rarely favored thymectomy to treat purely ocular MG in the absence of thymoma,[3] likely because of reluctance to recommend a major operation for symptoms such as diplopia and ptosis. Some surgeons[4] have countered this argument by advocating transcervical thymectomy as a less morbid and equally effective technique of resection as compared with the traditional transsternal approach. To date, a consensus has not been reached about the specific indications for surgery in the treatment of MG with symptoms limited to the eyes.

Opinion also varies as to whether ocular MG is a distinct disease or one end of a disease spectrum with severe generalized MG as the other end.[5] Because no definitive, prospective, randomized study has been conducted to resolve this issue, one must rely on sporadic reports with their inherent biases as well as on one's own experience. We have observed that the ocular symptoms of MG seriously impair patients' lifestyles, that there are serious side effects of the long-term use of potent drugs, and that progression to generalized MG is a bad outcome. We therefore have used thymectomy in MG even when symptoms have been purely ocular. We now report the results from two institutions in which thymectomy has been used to treat ocular MG.

Patients and Methods

Between 1970 and 1998, 61 patients underwent thymectomy for ocular MG (Osserman stage I), 54 patients at the University of Rome "La Sapienza" and 7 patients at the University of California, Davis, Medical Center. The hospital course of each of these patients was reviewed retrospectively. All patients had been referred from neurologists who had a specific interest and expertise in the management of MG. All patients with purely ocular symptoms who were referred for thymectomy were accepted for surgery. The diagnosis of ocular MG was made clinically with a

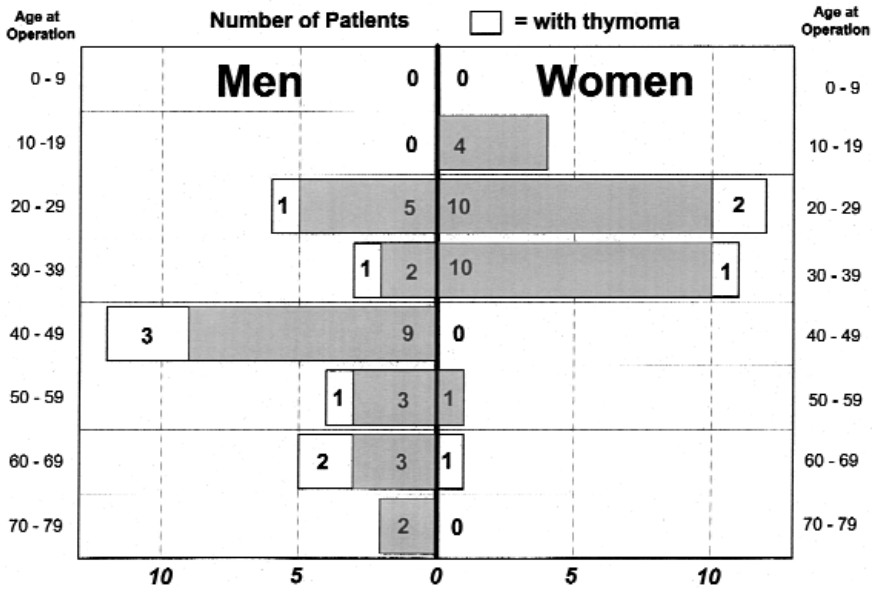

Figure 1. Distribution of patients with ocular MG.

detailed history and physical examination in all patients by an academic neurologist specializing in MG. Patients with only ocular symptoms were included. Adjunctive testing was also performed in all patients, including a combination of jitter testing, electromyographic testing, and acetylcholine receptor antibody assay.

Transsternal resections were done in 55 patients, including 17 full sternotomies, 38 partial sternal splits, and 6 transcervical resections. There were 30 women (49%) and 31 men (51%); mean age was 37 years (range 14–73 years; standard deviation ±15 years) (Figure 1). The records of all patients were reviewed. All surviving patients continue to be closely monitored by the principal neurologist. Additional updating was achieved through telephone interviews in cases in which more than 1 year had passed since the last visit. Preoperative management of the MG, duration of symptoms before the operation, pathologic findings of the resected specimens, and the immediate and long-term sequelae of operations were evaluated.

Definitions of Response

Patients who were symptom-free and did not require any further medication were designated as *cured.* Those who became less symptomatic than preoperatively or who needed less medication were categorized as *improved.* Patients whose postoperative symptoms and medications were similar to those experienced preoperatively were considered *unchanged.* Patients whose ocular symptoms or progression to generalized MG became exacerbated or who died as a result of the operation were categorized as *worse.*

Data were compared and analyzed for statistical significance by a Mann-Whitney rank sum test.

Results

All patients who underwent thymectomy without thymomas lived. The single operative complication leading to death in the study was postoperative bleeding in a patient with a thymoma. Two minor complications (3.3%) of pneumothorax, which necessitated chest tube placement, occurred after thymectomy. No postoperative wound complications were encountered.

Follow-up was complete in 100% of the patients. The mean duration of follow-up was 9 years (range 6 months–29 years). Thirty-one (51%) patients were cured (mean of follow-up 11 years; range 6 months–29 years). The condition of 12 (20%) patients was improved (mean follow-up 8 years; range 9 months–25 years). The condition of 16 (26%) patients was unchanged (mean follow-up 9 years; range 3-23 years). Two patients, including the 1 who died as a result of the operation, were in worse condition. Six patients subsequently died of unrelated causes (Figure 2).

Twelve (20%) patients had thymomas (stage I, 4 patients; stage II, 4 patients; stage III, 2 patients; and stage IV, 2 patients) (Table 1). Except for the single operative death, the outcome of patients with thymomas was similar to that of the whole group. Four patients died as a result of thymoma recurrence (mean 5.5 years; range 4–7 years).

Two patients received corticosteroids only preoperatively. All other patients received anticholinesterase drugs preoperatively and 12 patients received both. The average duration of symptoms before surgery was 9.5 months (standard deviation ±10 months; range 1–60 months).

Patients who were cured or improved after thymectomies were compared with those who had no benefit from thymectomy or became worse. All groups were similar with regard to age, duration of symptoms, presence of thymoma, and surgical approach.

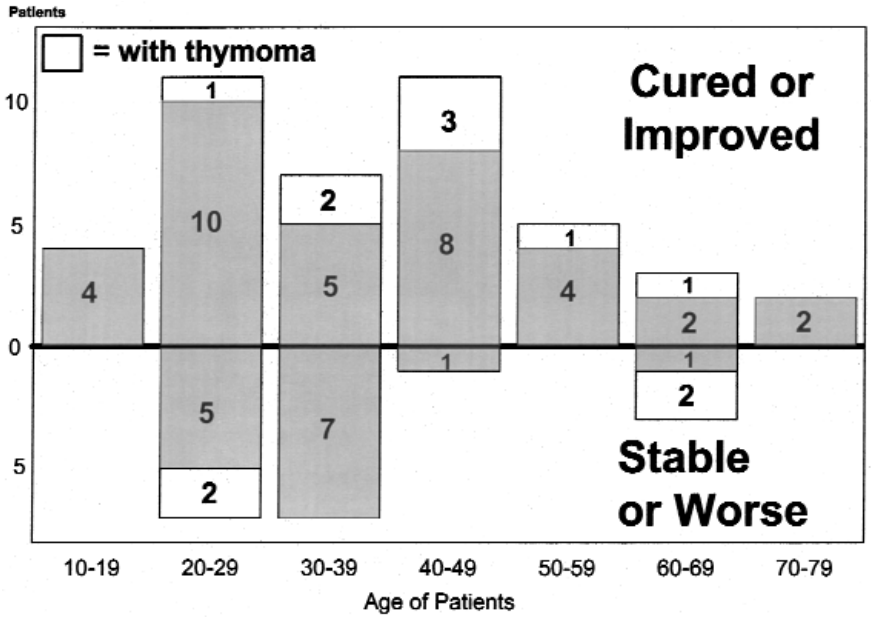

Figure 2. Response to thymectomy.

Discussion

Ocular MG is not a life-threatening illness and some natural remissions clearly occur without surgery. Oosterhuis[6] reported a natural remission rate of 30% in cases of ocular MG during the course of 15 years. Few large long-term studies have been conducted in patients undergoing thymectomy for purely ocular MG. Whether the route is transsternal or transcervical, thymectomy must be considered a major operation. Treatment of generalized MG with thymectomy has been scrutinized in the same way as thymectomy for ocular MG. However, the tremendous variability in diagnosis, medical treatment, and length of time before referral to a surgeon has made ocular MG difficult to study. Lack of a good database and reliance on referring neurologists for most follow-up information have been cited for the variability of the few published studies. In addition, because of the nuisance nature of the symptoms, patients themselves may not be reliable in retrospect for detailing the duration and intensity of their symptoms many months to years after the operation.

During the past 2 decades, conflicting conclusions have been reported about the best way to manage ocular MG. Schumm and colleagues[7] used an outcome scoring system and reported that all 18 of their patients treated with thymectomy had some improvement and that none had progression to generalized MG. Even though only 3 (17%) of their patients responded with full remission, the authors nevertheless recommended thymectomy to treat patients whose ocular MG failed to improve after 6 months of nonoperative management. Papatestas and associates[8] reported on 2062 patients with MG, including 962 patients who had thymectomies and 12 who had thymectomies for the treatment of ocular MG. They concluded that good outcomes from thymectomies for all stages of MG were most likely when operations were done early and when the patients did not have thymomas.

Evoli and associates[9] reported on 247 patients who underwent thymectomy for all stages of MG. After analysis of their data, they concluded that thymectomy is not effective in patients with purely ocular symptoms. However, they did not specifically evaluate the presence or absence of thymoma and duration of symptoms before treatment in the ocular subgroup. Their average duration of symptoms before surgery for all stages of MG was 15.9 months in those with a thymoma and 37.6 months in those without a thymoma (range 1–312 months). Hatton and coworkers[10] reported on 11 patients treated in a 15-year period and concluded that the therapeutic outcome of thymectomy for ocular MG was the same as that of nonoperative management. They also did not discuss the elapsed time from development of symptoms to operation. These data, combined with those of others,[11,12] fueled the belief that thymectomy should not be recommended for the treatment of ocular MG.[3] Proponents of thymectomy in the treatment of ocular MG, such as Nakamura and colleagues,[13] whose 22 patients had a postoperative remission rate of about 33%, and Masaoka and associates,[14] who unequivocally advocated thymectomy for the treatment of ocular MG, recommended radical thymectomy and found the duration of symptoms before the operation to be a predictor of outcome. Their mean duration of preoperative symptoms in patients not having a thymoma was 45.6 months (range 0–348 months [mean

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18.6 months; range 0–192 months in patients with a thymoma]). Table 2 summarizes previously published information.

Analysis of our data demonstrated no difference in duration of preoperative symptoms when comparing patients benefiting from surgery with those not benefiting from surgery. However, our mean duration from diagnosis to surgery was 9.5 months, which is much lower than that reported in other studies we examined. This shorter time span may help to explain why our results seemed better than those of other groups, even in studies that favored thymectomy for ocular MG.

We believe the evidence favors the treatment of ocular MG with thymectomy. Seventy-one percent of our patients with ocular MG were cured (51%) or improved (20%) after thymectomies. Even if we assume a natural remission rate of somewhere between 10% and 30%, the 51% cure rate and additional 20% improvement rate in our study cannot be discounted and must be attributed to a surgical effect. None of the patients with ocular MG without thymoma had adverse sequelae from their operations. The patient who died postoperatively had a thymoma, which by itself would have been an indication for the operation.

On the basis of previous reports about the adverse effect of thymoma on the outcome of thymectomy, we expected less favorable results among our patients having ocular MG with thymomas. Sixty-seven percent of the 12 patients in our thymoma subgroup were cured (33%) or improved (33%), but this percentage was not statistically significant ($P < .39$) when compared with the percentage of patients cured in the ocular MG group without thymoma. However, the number of patients in our thymoma subgroup was not large. Possibly a larger study of patients with ocular MG and thymomas could provide more definitive data, but such a study will require a prospective, randomized, cooperative trial.

The relation between thymoma and MG is a fascinating and incompletely understood issue in tumor biology. At least two factors may explain why our results were better than previous ones. First, our collective patients were operated on soon after the onset of symptoms. Second, after the operation, neurologists did not hesitate to withdraw all drugs if gradual improvement to resolution of symptoms occurred. This certainly contributed to our high cure rate. Some surgeons have cited neurologists' reluctance to withdraw medication in symptom-free patients as a contributing factor in lower cure rates. Maintenance of drug therapy is based on the belief that continuation of some drugs may help prevent recurrence of MG symptoms. There is some immunologic evidence that thymectomy in the presence of thymoma may exacerbate MG symptoms and that drugs should be continued regardless of symptomatic improvement.[15,16] Good evidence exists to suggest that, in the future, specific immunotherapy will be a crucial part of the treatment of MG.

However, according to our data, in the majority of patients thymectomy affords a chance of complete remission, improvement in symptoms, decreasing medication dosages, and the potential of halting progression to generalized MG. Even the 16 patients in our group whose conditions we categorized as unchanged may have actually received some benefit given the overall very low rate of progression to generalized MG (1.6%). With only 3.2% of patients in worse condition and an operative mortality and serious complication rate of 1.6%, there is little risk in pursuing surgical management.

Thymectomy is a major operation whether done through the neck or the sternum. The optimal technique is the subject of many past and ongoing studies and is beyond the scope of our article. Our rationale for performing thymectomies was based on the observation that the symptoms of ocular MG do interfere significantly with the lifestyle of patients and on the fact that significant risks and costs are associated with long-term nonoperative treatment. Inasmuch as one of our patients died of postoperative complications, one could argue that thymectomy is not entirely safe. However, this single death occurred in a patient who had a thymoma for which thymectomy would have been recommended even without MG. Because no deaths or major complications occurred among patients who had pure ocular MG without thymomas, the argument seems less sound.

If we analyze our patients without thymomas, we have a subset of patients with a 71% rate of improvement or cure and a 0% operative mortality. On the basis of our results, we think thymectomy should be considered for patients with ocular MG in all age groups if there is a reasonable life expectancy and comorbidities are not significant. Approach by the transsternal or transcervical route is safe and will likely be effective in the majority of patients, regardless of age or preoperative duration of symptoms.

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Discussion

Dr James B. D. Mark *(Stanford, Calif).* Dr Roberts has presented some interesting and provocative material. It now behooves us to see just how compelling his argument is. What he wants us to do is to seriously consider thymectomy as the primary treatment for ocular MG, a position quite contrary to the prevailing opinion in this country. Let us dissect his argument.

This report concerns 61 patients operated on over a 20-year period in two institutions, one in California and one in Italy, both locations well known for wine and joie de vivre. The first thing that strikes the eye is that 54 of the patients were operated on at "La Sapienza" in Rome and 7 at UC Davis, suggesting strongly that there may be a bias toward thymectomy for ocular MG outside the United States and very little enthusiasm for it in this country. A review of the literature reinforces this idea. In any study such as this, it is impossible to know how many patients with ocular MG were never referred for surgical opinion, which in this study was tantamount to surgical treatment.

Why do these authors operate on patients with MG while most groups do not? Twelve of 61 patients had thymoma. No one argues against operation in those patients, but how about the others? The reasons offered by the authors and others are to alleviate the symptoms of ocular MG, to avoid the adverse effect of drugs used to treat MG, to accelerate the onset of remission, to prevent progression to generalized MG, and to decrease mortality.

How compelling are the arguments? Ocular MG affects the extraocular muscles and the levator palpebrae leading to diplopia and ptosis. Diplopia can be palliated by patching one eye at a time. No binocular vision, no diplopia, as the old saying goes. Ptosis is a bit more of a problem, but a relatively minor palliative operation, surely not as invasive or risky as thymectomy, is available for that problem. The worst symptoms are usually in the first year after onset, so most treatment does not have to last forever. Twenty percent to 50% of patients with ocular MG have a remission without an operation. In the absence of a controlled study, it is unlikely that one can prove that surgery hastens remission or results in more remissions than medical treatment. Essentially all neurologists in this country recommend medical treatment of ocular MG for 1 year before surgical treatment is considered. In the present study, 9½ months was the preoperative period—not very different from 1 year. If the disease becomes generalized during that period, then thymectomy is in order, but that occurs in only 15% of patients who still have only ocular symptoms after 1 year. Another 20% have experienced remission during that year. In the series from Mount Sinai in New York reported by Papatestas, 300 patients had ocular MG and no thymoma, only 3 of whom were treated with thymectomy. One of the 3 went into remission and another died, illustrating the chilling effect of an early death after elective, even controversial, surgery. The 1 death in the operative series reported today occurred in a patient with thymoma who would have been operated on for that reason alone and should not be a vote against thymectomy for ocular MG. Although it is true that powerful drugs such as pyridostigmine bromide (Mestinon), prednisone, and azathioprine may and do cause adverse effects in 50% or so of patients, the drugs had to be stopped in only 1% to 14% of patients in a series reported from The Netherlands.

I would like to say a word about operative technique. The most important thing is complete removal of the thymus gland. My own preference was for sternotomy. I thought I could do the best job that way. If others can accomplish complete thymectomy using a cervical or even thoracoscopic approach in patients without thymoma, well and good. I do not believe Jaretzky's so-called maximal thymectomy is necessary.

In summary, I find the information interesting but not scientifically persuasive. What Dr Roberts has described is a phase II study demonstrating feasibility. What we need is a phase III study so that the best treatment of ocular MG can really be identified.

Dr Roberts. Thank you very much, Dr Mark. I certainly concur with your comments. You have given an elegant discussion of the more detailed problems that face the treatment of patients with MG. Chief among them is the absence of any prospective, randomized study. Until such a study can be organized, we will have to rely on sporadic reports from various studies, but certainly your points are valid. What our report did demonstrate is that surgical treatment is safe, with a low complication rate and a very low mortality rate, and still provides these patients with a 70% chance of cure or improvement. The rate of progression of 10% to 20% to generalized MG is probably pretty low. In our group it was virtually 0%.

I appreciate your comments and I look forward to a greater consensus on the treatment of this disease.

Dr Thomas W. Rice *(Cleveland, Ohio).* This study covered a large span of time and it was performed at two different institutions. How did you diagnose MG? How did you define ocular MG? How did you exclude diffuse or truncal MG?

Dr Roberts. Diagnosis is another of the difficulties in this disease. If the patient is having a "good day," when he or she feels a little lethargic or feels great, the patient may claim to have no other symptoms. That may change the diagnosis. All the patients were referred by neurologists who specialize in the diagnosis and treatment of MG. A combination of methods was used, largely assessment of symptoms, both ptosis and diplopia. There was no specific grading system within those two. There was some variability in provocative testing and electromyography.

Dr Rice. Are you saying that the majority were categorized just by their symptoms?

Dr Roberts. They were categorized by their symptoms and by provocative testing.

Dr Rice. Is it true that electromyography was not used?

Dr Roberts. The Italian group actually did use electromyography in all but a couple of their patients.

Dr Rice. In how many of the patients did the disease progress?

Dr Roberts. One.

Dr Rice. Did you subclassify thymomas into cortical or medullary?

Dr Roberts. Yes. All but 4 were cortical; I believe those 4 were of a mixed subtype.

Dr Rice. Did that predict stage or survival?

Dr Roberts. No, there were only 4 such cases. The predictor of death was the stage of disease, and all patients with stage III or IV MG died within 5 to 7 years.

Dr John Chen *(Honolulu, Hawaii).* The timing of thymoma for ocular MG has been somewhat controversial. You did not specify at what point you did the operation. During your review of these patient records, did you encounter a time period in which patients were monitored, or were they operated on at the time of referral?

Dr Roberts. All of the patients in both groups were operated on after they were referred by the neurologist, but the neurologist largely determined when the operation would be done by the timing of that referral. On average, though, surgery was not considered before 6 months.

Dr Richard Whyte *(Stanford, Calif).* Can you describe the specific indications for the referral for the operation, or did the neurologist, particularly those in Italy, just say, "If the patients have ocular MG, they should have an operation?"

Dr Roberts. That is largely true, and I think that is why the Italian group had as large a number of patients as they did. Our patients were referred by a single neurologist who believes that ocular MG that does not resolve in less than 6 months with anticholinesterase therapy should be treated by thymectomy. That essentially was the indication for operation.

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