The Value of Thymectomy in Myasthenia Gravis:

A Computer-Assisted Matched Study

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In the absence of a prospective randomized study of patients treated conservatively or with thymectomy, a computer-assisted retrospective matched study was devised. Of 563 patients treated for myasthenia gravis without thymoma up to 1965, 104 had thymectomy. With computer assistance, each surgical patient was matched with a medical patient on the basis of age, sex, and severity and duration of disease. On this basis 80 of the 104 surgical patients could be matched satisfactorily. There were 16 males and 64 females in each of the matched surgically treated and medical control groups. A complete remission was experienced by 27 of the 78 patients in the surgical group as compared to 6 of the medical group. Improvement was noted by 26 of 78 surgically treated patients and 13 of 78 receiving medical treatment. Survival curves show a significantly better chance of long-term survival for patients having thymectomy. Thirty-four patients in the medical group had died as compared to 11 in the surgical group. Comparison of survival in relation to sex, duration of symptoms, or age (<30 or >30 years) did not show a significant difference. Until more effective treatment is available for myasthenia gravis, thymectomy deserves consideration for both sexes, and with increased age or long duration of symptoms.

THYMECTOMY in the treatment of myasthenia gravis has gained surprising acceptance whereas the etiology of the disease has been so elusive and the basis for operation so empirical. The impetus provided by the report of Blalock and associates[2] in 1939 has been sustained in spite of conflicting reports over the selection of patients for surgery and the relative value of medical and surgical treatment. Good efforts to compare these two modes of therapy have been published[5,6,13,15] but all lack the virtues of a randomized prospective study. With the certain knowledge that such a study would not be entertained in our institution and in an effort to improve retrospective review, we have selected matched groups of medically and surgically treated patients with computer assistance.

The retrospective selection of patients for review was made more palatable by the fact that all of the patients had been examined by a few neurologists with special interest in myasthenia gravis and with a uniform method of assessment.

Materials and Methods

Five hundred sixty-three patients treated at the Mayo Clinic up to 1965 for myasthenia gravis and without evidence of thymoma were studied. Complete followup data to 1969 were available on all these patients. Patients less than 17 years of age at the onset of disease were excluded from the study, results of treatment for this group having been reported earlier.[14] Of 563 patients, 104 had undergone thymectomy as part of their treatment of myasthenia gravis. All thymectomies were carried out by median sternotomy.

Using the IBM 370 computer, we matched each surgical patient with a medical patient according to age and sex

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TABLE 1. *Age Distribution by Decades and Sex of 160 Patients With Myasthenia Gravis*

	Surgical Group (80)		Medical Group (80)	
Age (yr)	M	F	M	F
17–20	3	16	3	16
21–30	2	29	2	29
31–40	5	13	5	13
41–50	4	4	4	4
51–60	0	2	0	2
>60	2	0	2	0

TABLE 3. *Status (to 1974) in Matched Groups*

Status	Surgical Group (80)	Medical Group (80)
Complete remission	27	6
Improved	26	13
Unchanged	3	7
Worse	1	5
Dead	21	47
Myasthenia gravis	11	34
Other causes	10	13
Lost to followup	2	2

as well as severity and duration of disease. Medically treated patients who most closely matched the surgical patients were selected by the computer. With these criteria, 80 surgical patients could be matched satisfactorily with a medically treated patient. The present status of the 160 patients in the two matched groups was ascertained by reexamination and written questionnaire with or without a telephone call to the patient and home physician.

Each patient was classified in one of the five following categories depending on the present status: 1) remission; 2) improved; 3) unchanged; 4) worse; and 5) dead. Remission occurred when the patient required no medication and had no symptoms of myasthenia gravis except in rare instances when a mild inconstant deficit was present. The patient was considered improved if less medication was required than on the previous clinic evaluation and if the handicap from the disease was less. If the changes were minimal or equivocal, the status was considered unchanged. Death was designated as related to myasthenia gravis if it occurred after progressive weakness and respiratory failure in the absence of other significant disease.

Clinical Features

Each group—the surgically treated group and the medical control group—had 16 males and 64 females. The average age at onset of myasthenia gravis was 29 years for the surgical patients and 30 for the medical patients. Table 1 shows the distribution of the patients by age and by sex.

Seventy-eight of the patients in each of the matched groups had moderately severe symptoms of myasthenia gravis. Only two patients had ocular symptoms alone, which would not be an indication for thymectomy according to our present philosophy. Table 2 shows the distribution of weakness found on physical examination in each of the 160 patients when they were first seen at this clinic.

TABLE 2. *Physical Signs*

Findings	Surgical Group (80)	Medical Group (80)
Ocular weakness	73	65
Throat weakness	65	64
Upper extremity weakness	72	55
Lower extremity weakness	58	45
Trunk weakness	46	28

Results

Complete remissions were noted in 27 of the thymectomized patients and in only 6 of those treated medically (Table 3). Another 26 of the surgical patients were improved as compared to 13 of the medical group. Five of the medical patients but only one of the surgical patients were worse. The average duration of followup for those alive to 1974 in the surgically treated patients was 19.5 years compared to 23 years in the medically treated group. Twenty-one of the surgical group have died, myasthenia gravis being the cause of death in 11. The hospital (postoperative) mortality rate was 6%. Forty-seven patients in the medical group have died, 34 because of myasthenia gravis. The average time of death after onset of myasthenia gravis in the medical patient was 7 years as compared to 10 years for the surgical patient.

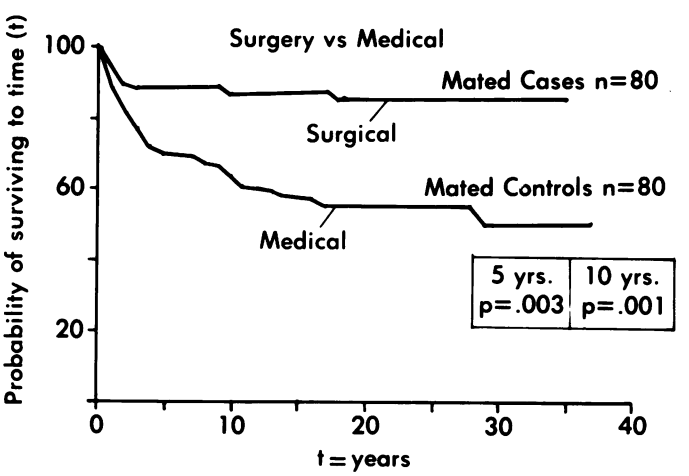

FIG. 1. Survival curve. Effect of thymectomy.

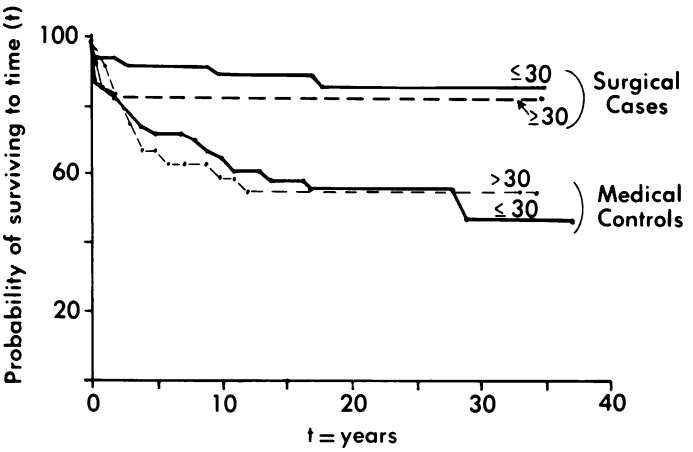

FIG. 2. Survival curve. Age.

A more accurate way of interpreting the effect of surgery on patients having myasthenia gravis is to analyze the statistical differences in their survival by drawing survival curves for the two matched groups. By this method of analysis, death due to causes other than myasthenia gravis has been regarded as the same as lost to followup at the time of death. Figure 1 shows that thymectomized patients have a significantly better chance of surviving 5 years (P = 0.003) and 10 years (P = 0.001).

Age. In the surgically treated patients the survival was no different whether the onset of their symptoms was before or after age 30. This lack of significance may be due to the small sample available for study. However, the survival rate was higher in both younger (P = 0.001) and older (P = 0.02) surgical patients compared to medical patients (Fig. 2).

Duration of Symptoms. The duration of symptoms did not have a significant influence on long-term survival.

Influence of Sex and Relationship of Thymectomy. In the matched surgical group, comparison of survival in relation to sex did not show any significant difference (Fig. 3). However, the survival experience of females was significantly better in the surgical group than in the medical group (P = 0.011). Although the males were also found to have a more favorable survival in the surgical group, this difference was not statistically significant, probably because of the small sample (16 patients).

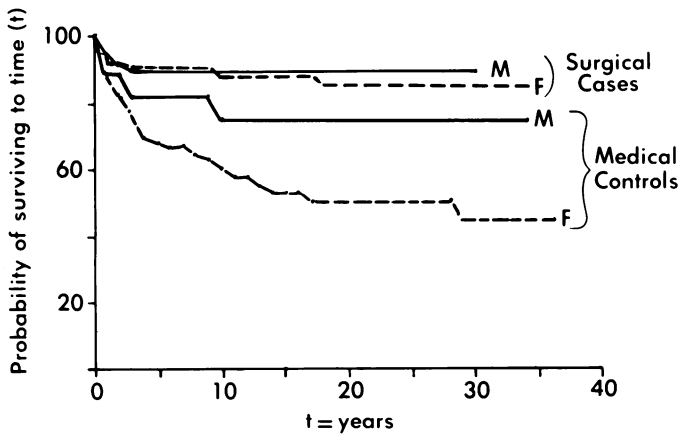

FIG. 3. Survival curve. Influence of sex.

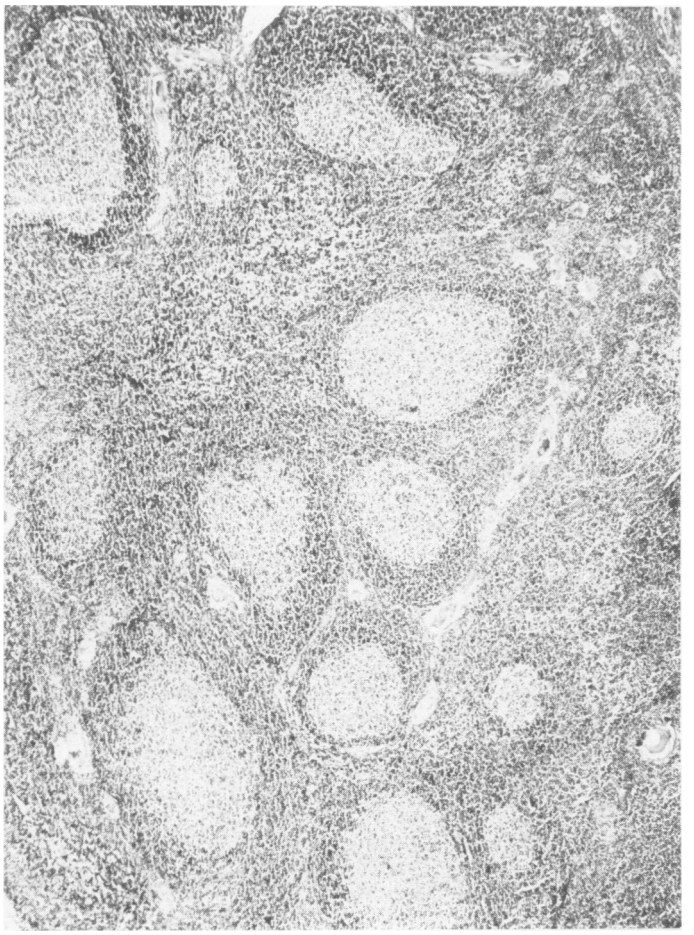

FIG. 4. Severe hyperplasia. Note total, or almost total, lymphoid tissue with prominent germinal centers (H & E ×47).

Histologic Aspects

Thymic glands of 66 of the 80 surgically treated patients were available for review. Microscopic features that were noted were the degree of hyperplasia, number of germinal centers, amount of calcium present in Hassall's corpuscles, and number of clear cells.

Hyperplasia was divided into three categories: severe thymic hyperplasia, atrophic or normal thymic glands, and moderate hyperplasia (which is intermediate between the two types) (Figs. 4 and 5). The longer survival of those patients with severe thymic hyperplasia (Fig. 6) was statistically significant (P = 0.02) compared to those with atrophic or normal glands. Similarly, the longer survival of those patients who had four or more germinal centers

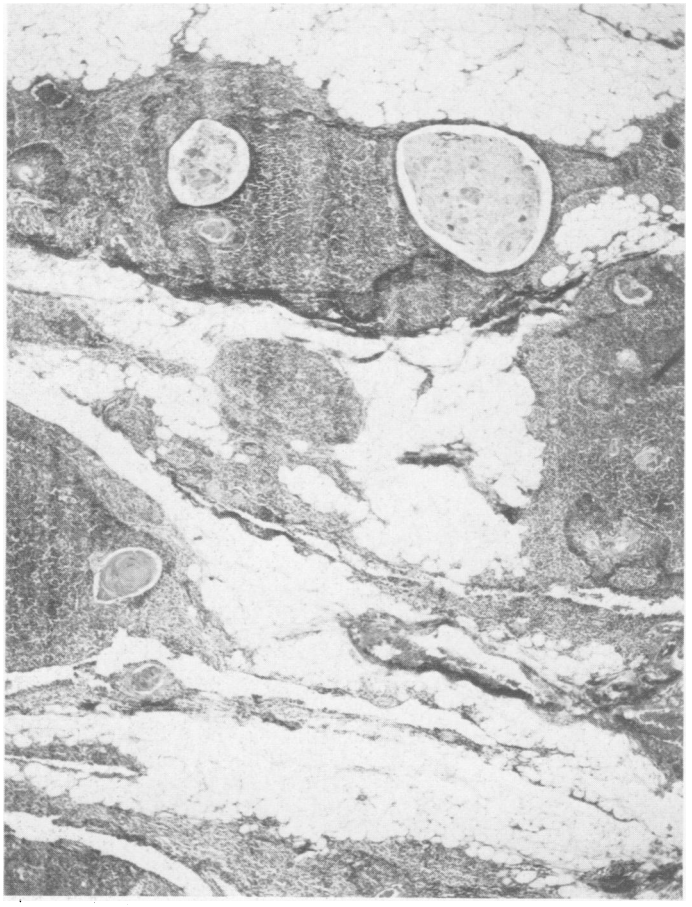

FIG. 5. Atrophic or normal thymus. Marked to moderate replacement of thymic tissue by adipose tissue, with either no or few germinal centers (H & E ×47).

per low-power field (Fig. 7) was statistically significant ($P = 0.01$) compared with those with 0 to 1 germinal center. Other histologic criteria such as the amount of calcium in Hassall's corpuscles or the number of clear cells did not influence survival.

Discussion

A cloud of uncertainty has hovered over the empiric treatment of thymectomy for myasthenia gravis, but evidence has accumulated gradually to provide sustenance for such advice in selected patients. Although a relationship between the thymus and myasthenia gravis was suggested by Weigert[16] in 1901, it was not until 1939 that Blalock and associates[2] described delayed improvement in a patient with the disease who had a cyst removed from the region of the thymus. This was hardly a firm basis for surgical aspirations, but impetus for the surgical treatment of myasthenia gravis was certainly provided by that paper. Keynes[8,9] of Great Britain was an early and firm advocate of thymectomy, and Clagett and Eaton[3-5] of this clinic supported the concept with some conflict in results related to selection of patients, largely whether or not a thymoma was present. Surgical interest has been maintained, and reports of large groups of surgical patients have been compared to patients treated medically, with the general conclusion that thymectomy had the most to offer for the young female patient with myasthenia gravis of short duration.[6,13,15]

Different correlations between thymic pathology and prognosis after thymectomy for myasthenia gravis have been reported. MacKay and associates[11] correlated the presence of thymic follicular hyperplasia with a good response to surgery and its absence to a poor response. Genkins and associates[7] and Alpert and associates[1] found that delayed remission after thymectomy was related to the presence of thymic hyperplasia and that patients with more germinal centers in their thymus survived longer. In our study the longer survival of patients with severe hyperplasia was statistically significant.

As suggested previously, comparison of these matched groups indicates that thymectomized patients with myasthenia gravis do have a significantly better chance

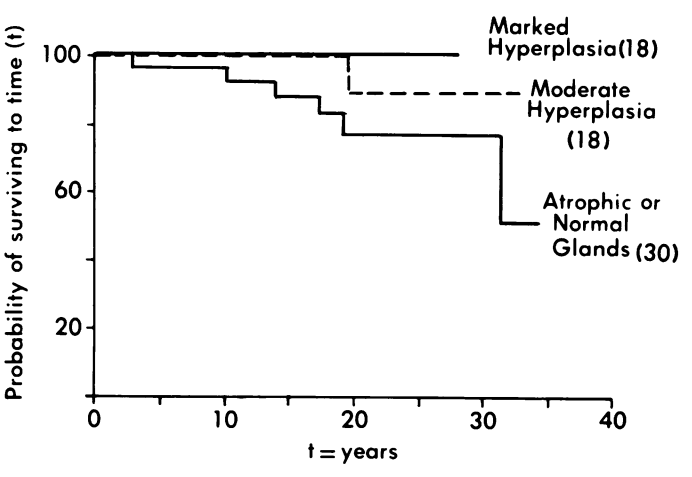

FIG. 6. Survival curve. Hyperplasia.

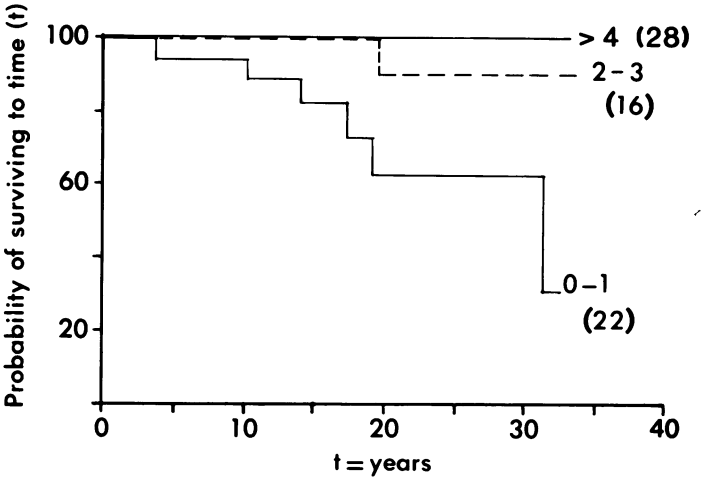

FIG. 7. Survival curve. Number of germinal centers.

for long survival. In the past we emphasized the improved candidacy of the young female with myasthenia gravis of short duration. Our present observations suggest that the guidelines for surgical treatment should be liberalized. The survival of patients 30 years of age or older treated by thymectomy probably does not differ from that of patients 30 years of age or younger, but both groups, regardless of sex, had considerably better survival rates than patients treated medically. The philosophy of offering early thymectomy to a greater range of patients with myasthenia gravis with respect to age, sex, and duration of disease has been expressed recently by others.[7] Improved management of respiratory complications in patients with myasthenia gravis has resulted in significant improvement of postoperative morbidity and mortality.

The cause of myasthenia gravis has been elusive, but evidence concerning the type of neuromuscular defect in the disease and its probable autoimmune nature stimulates association with the thymus, whose role in immunosurveillance, autoimmune disease, and neuromuscular transmission has gained more and more experimental confirmation.[12] Now purification of receptor proteins from the electric organ of the electric eel has been demonstrated as having the potential of inducing a state in experimental animals similar to myasthenia gravis in humans.[10] It seems likely that future discoveries will permit the management of myasthenia gravis without surgical intervention but, for the present, the beneficial role of thymectomy for these unfortunate patients has been clearly demonstrated. It would seem extremely important that we employ comprehensive prospective immunologic surveillance of these patients in an effort to clarify the role of the thymus in myasthenia gravis. The relative importance of antibody and cell-mediated immunity in the etiology of myasthenia gravis remains uncertain.

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Discussion

Dr. Earle Wayne Wilkins, Jr. (Boston, Massachusetts): I share with the authors of this excellent study their concern that confirmation of the value of thymectomy in the treatment of myasthenia gravis has indeed been elusive. Our efforts at the Massachusetts General Hospital in justifying the procedure have been along the lines of a collaborative study with the Mount Sinai group in New York City, in which we have attempted to compare 267 patients undergoing thymectomy with 417 treated medically. As in their study, we excluded all patients with thymoma.

This slide is not as complex as it looks. These 225 patients survived long enough to have a comparison made. Along the left are the preoperative classification, and across the top the final evaluation, (A) being a total remission, (1) pure ocular disease, (2) a mild systemic disease, and so on in more increasing extremes of the disease.

You will note that most of these patients are in moderate to severe systemic disease, or worse. The dotted squares on the diagonals indicate the patients who were basically unchanged by surgery. All those above and on the right are worsened. Those below and on the left are improved. And at the bottom are the results.

(Slide) Now, contrast this with the patients treated medically. Note that many more of these were of lesser extent of disease, and that the improved group really was a total of only 28%, as compared with the 80-odd per cent in the thymectomized group.

Now, perhaps a better way of comparing our results with the present series today would be to include those who died and were otherwise lost to followup. Our total of remission or improvement, thus, is 76%, which compares very favorably with the figures reported today. Our total death rate is 14%, which, as I calculated from the protocol, was identical with theirs.

There is no question that their computerized study is a far better approach to comparison of the thymectomized and the conservatively treated patients than ours, but I would ask the authors: Is this good enough? Have we totally eliminated bias? Have we totally disproved the possibility—as Henry Beecher, our chief of anesthesia, used to challenge us—"is this a placebo operation?"