Myasthenia gravis: clinical and histological features in relation to thymectomy

M. A. SAMBROOK, H. REID, P. D. MOHR, AND H. G. BODDIE

From the University Department of Neurology, Manchester Royal Infirmary, Manchester

SYNOPSIS The clinical and thymic histological features of 23 patients who underwent thymectomy for myasthenia gravis have been examined and compared. Eighty-two per cent of patients with a non-neoplastic gland containing numerous germinal centres improved postoperatively, whereas 83% of patients with a non-neoplastic gland containing no germinal centres deteriorated or died. Glands with only slight involution and containing numerous germinal centres were more commonly seen in young female patients. The evidence relating thymic histological appearances with the postoperative progress of patients with myasthenia gravis is reviewed.

An association between myasthenia gravis and the thymus gland was first suggested by Weigert in 1901. Although Schumacher and Roth (1913) reported the clinical improvement of a patient with myasthenia after removal of an enlarged non-neoplastic gland, it was not until the reports of Blalock et al. (1939) and Keynes (1949) that the beneficial effect of thymectomy was fully appreciated. Keynes concluded that, although the connection between myasthenia and abnormalities of the thymus gland was well established, there was no clue to how or why the gland acquired its abnormal function.

Only recently have the histological appearances of the thymus gland and their relation to the clinical progress of patients after thymectomy received greater attention (Castleman and Norris, 1949; Mackay et al., 1968; Alpert et al., 1971; Seybold et al., 1971; Reinglass and Brickel, 1973; Vettes and Simpson, 1974). Opinions have varied from a clearly demonstrable association between thymic hyperplasia and postoperative improvement to a complete dissociation of these two parameters. It therefore seemed appropriate to make a clinical and pathological study of 23 myasthenic patients who had undergone thymectomy at the Manchester Royal Infirmary during the past 10 years.

METHODS

PATIENTS Twenty-three patients with myasthenia gravis underwent thymectomy. Surgery was performed because of either increasing weakness despite treatment with anticholinesterases and in some cases steroids (19 patients) or the presence of a thymoma (four patients). At the time of operation all patients had evidence of ocular, bulbar, and limb weakness.

The average age at onset of symptoms of patients without a thymoma was 32.6 years (range, 16–68 years) and the mean duration of symptoms before thymectomy was 4.9 years. The sex distribution showed a predominance of females with a ratio of 2.2:1. Patients with a thymoma developed symptoms at 39, 49, 56, and 65 years and the mean preoperative duration of symptoms was 1.0 year. Three of these patients were male.

HISTOLOGY Haematoxylin and eosin stained sections from all the paraffin blocks from each surgical section were examined by one of the authors (H.R.) without knowledge of the clinical details. The average number of sections to each specimen was three with a range of two to 10. The criteria used for assessment included the degree of gland involution, the overall cellular composition and frequency of plasma cells, the frequency of germinal centres, the epithelial cell type, and the presence of perivascular lymphocytic cuffing or lake formation. The grading system used for these criteria was that of Alpert et al. (1971). The overall cellularity of the glands was estimated by comparison with sections from non-myasthenia thymectomy specimens from pat-

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patients of approximately the same age removed at the onset of operation for cardiac or chest surgery.

RESULTS

Myasthenia and thymoma

Four patients had a thymoma and all received preoperative radiotherapy. Postoperatively, two patients improved, one becoming virtually asymptomatic, while the remaining two showed no improvement.

All of the four surgically removed specimens contained a thymoma, three of which were of the epithelial type and one of the lymphoid type. One of the epithelial thymomas was considered to be of low grade malignancy. Residual thymic tissue was present in three specimens, none of which had germinal centres.

No correlation between the histological findings and the clinical progress of the patients could be made.

Myasthenia not associated with thymoma

PROGRESS AFTER THYMECTOMY For the purpose of clinical assessment patients were divided into three groups based upon their progress after thymectomy:

Group A—Complete remission or marked improvement.
Group B—Significant improvement.
Group C—No improvement, deterioration, or death.

Patients were reviewed at regular intervals and details of their most recent assessment, duration of follow-up, sex distribution, pre- and postoperative treatment, and allocation into these three groups are included below and in Table 1. The mean preoperative duration of symptoms and the sex ratio varied among the three groups but this probably reflected the small number in one of these groups. When those patients who had improved (groups A and B) were compared with those who had shown no improvement or had deteriorated (group C) the ratios for these factors were not significantly different (Table 1).

The mean age at onset of symptoms increased from group A (23.1 years) to group C (42.6 years). The postoperative interval before reaching group A ranged from six months to 2 ½ years. In six of the eight patients it was less than 12 months and in the other two it was 15 months and 2 ½ years.

Group A (eight patients) One patient had a complete remission and was able to stop all anticholinesterase medication within four years of thymectomy. The remaining patients had improved markedly and were able to lead a fully active life with no restrictions. One patient had further improved with alternate-day prednisolone therapy and the improvement had been maintained on a maintenance dose of 10 mg on alternate days.

Group B (three patients) These patients had
improved significantly but were still limited by their weakness. Two of them had been operated upon only nine months before assessment and were still improving, while the clinical state of the third patient who had undergone thymectomy 2½ years previously had remained the same for at least 12 months. One patient had benefited from a five-day course of tetracosactrin (Synacthen) 1 mg daily.

Group C (eight patients) Two patients in this group had shown no overall change when compared with their state immediately before thymectomy. Both had deteriorated shortly after thymectomy but improved again after a five-day course of tetracosactrin.

There were no immediate postoperative deaths. Six patients died within two months to five years after thymectomy. Three steadily deteriorated postoperatively and terminally had recurrent bronchopneumonia and respiratory failure. Two of these patients died in 1964 and 1966 and did not receive steroids, while a third continued to deteriorate despite their use. Three patients improved for periods ranging from two to 14 months after surgery. Two died suddenly at home, while the other patient had a more prolonged deterioration dominated by recurrent chest infection and the need for long periods of mechanical ventilation. Five-day courses of tetracosactrin were used postoperatively in this last patient and resulted in some temporary improvement but failed to have any permanent benefit.

One patient had a breast lump biopsied at the time of thymectomy which was subsequently found to be malignant and a simple mastectomy was performed several days later. There was no clinical or electromyographic evidence to indicate that this patient had the Eaton-Lambert syndrome.

HISTOLOGICAL FINDINGS Nineteen non-thymomatous glands were examined. The extent of involution was assessed as slight in eight specimens (42%), moderate in seven (37%), and severe in four (21%). Germinal centres were numerous in 11 specimens (58%), and the extent of involution was slight in eight of these and moderate in the remainder. Two (11%) had occasional germinal centres in association with moderate involution and six (31%) had no germinal centres with either moderate (two) or severe (four) involution.

The overall cellularity showed a lymphocytic predominance in 12 (63%) specimens, an epithelial predominance in one (5%) and a normocellular appearance in six (32%). Plasma cells were rare in the majority (68%) of specimens, occurred occasionally in four (21%), and were numerous in two (11%). No correlation was found between lymphocytic predominance or an increased plasma cell frequency and those glands with numerous germinal centres. The epithelial cells were all of the plump type and only six specimens (32%) showed perivascular lymphocytic cuffing; none showed lymphocytic lakes.

COMPARISON OF CLINICAL AND HISTOLOGICAL FINDINGS The predominant cell type, incidence of plasma cells, and frequency of perivascular lymphocytic cuffing were not significantly different between each of the three clinical groups. The extent of involution of the thymus gland was more variable, however. In group A, five

### TABLE 2

| Age at Onset of Symptoms and Sex in Relation to the Thymic Histological Findings in 19 Patients with Non-Thymomatous Myasthenia Gravis |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| **Germinat centres** | **Involution** | | |
| | Numerous | Occasional | Absent | Slight | Moderate | Severe |
| No. of patients | 11 | 2 | 6 | 8 | 7 | 4 |
| Mean age at onset (yr; range) | 24.8 (16-36) | 21 & 40 (19-69) | | 24.5 (16-36) | 25.9 (16-40) | 61.0 (47-69) |
| % Females | 82% | 50% | 50% | 100% | 57% | 75% |
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![Graph](http://jnnp.bmj.com/)

**FIG. 1** The extent of gland involution in relation to the clinical grouping in 19 patients with non-thymomatous myasthenia gravis. Thymus gland involution: = slight, = moderate, = severe.

of the eight glands and in group B, one of the three glands showed only slight atrophy and in the remainder it was described as moderate. None of the glands in groups A and B was severely atrophic and this contrasted with group C where 50% had undergone marked involution (Fig. 1).

The incidence of germinal centres was the most notable histological feature. Ten of the eleven patients with glands showing numerous germinal centres had experienced either a moderate or marked improvement within nine months of thymectomy and at their most recent follow-up two patients in group B have further improved to join group A (Fig. 2). Two patients with this histological picture died at two months and five years after thymectomy. Five of the six patients with thymus glands containing no germinal centres failed to improve or died.

The age at onset of symptoms and the percentage of female patients varied among the different pathological groups (Table 2). The mean age of those patients with numerous germinal centres or slight gland involution was less than that for patients in whom germinal centres were absent or the gland was atrophic.

**DISCUSSION**

Sloan (1943) made a histological study of the thymus gland in 10 patients with myasthenia gravis and demonstrated that all the non-neoplastic glands contained an increased number of lymphocytes and that 70% had germinal centre hyperplasia. These appearances were not specific, however, and were also described in patients with hyperthyroidism, Addison's disease, acromegaly, and systemic lupus erythematosus (Sloan, 1943; McEachern and Parnall, 1948; Mackay and de Gail, 1963). Castleman and Norris (1949) confirmed these histological findings in myasthenia gravis and went on to relate the extent of germinal centre hyperplasia to the patient's postoperative progress but failed to demonstrate any correlation. Their results have been widely accepted, but it is notable that their index of clinical improvement was based primarily upon the postoperative decrease in neostigmine requirements and that the four patients who had improved most belonged to the group with the largest number of germinal centres.

Interest was reawakened by the suggestion of Goldstein (1966) that the thymic histological appearances were representative of an autoimmune reaction in the thymic medulla which caused the release of a neuromuscular blocking agent. Corroborative evidence came from the study of Mackay et al. (1968) which showed germinal centre hyperplasia to be most frequent
in young females with non-involuting thymus
glands who respond well to thymectomy. How-
ever, further reports have failed to confirm these
results. Alpert et al. (1971) found that patients
with germinal hyperplasia improved less fre-
quently after thymectomy than those with
occasional or absent germinal centres, although
this could not be confirmed statistically. There
was, however, a correlation between the degree
of thymic hyperplasia and the length of the post-
operative period before remission. On the basis
of this observation they suggested that neuro-
muscular injury was mediated by thymic lympho-
cytes and the time required for them to disappear
from circulation and for the patient to improve
was proportional to the extent of thymic hyper-
plasia. Seybold et al. (1971) studied the thymic
histological appearances in 43 juvenile myas-
thenics. Ninety-five per cent of the specimens
showed evidence of hyperplasia, the extent of
which could not be correlated with the remission
rate. It is difficult to compare their results with
those of Mackay et al. (1968) since the patients
studied were much younger and nearly all had
thymic hyperplasia compared with only half of
the patients in the earlier study. Reinglass and
Brickel (1973) were also unable to demonstrate
any relationship between the thymic histological
appearances and clinical progress in 12 thymec-
tomized patients but, on analysis of their results,
it is noteworthy that the only patients who im-
proved greatly or underwent a remission had
marked germinal centre hyperplasia. Finally,
Vetters and Simpson (1974) made a quantitative
histological study and demonstrated a tendency
for patients with relatively 'unreactive' thymus
glands to improve most after thymectomy but
again this could not be confirmed statistically.

The present study includes 23 patients who
have had a thymectomy during the past 10 years.
Adequate histological material was available and
sections were examined without any knowledge
of the clinical findings. Eighty-two per cent of
patients without a thymoma who had undergone
a complete remission or improvement (groups A
and B) had numerous germinal centres whereas
only 25% of those who remained the same, de-
teriorated, or died (group C) had this histo-
logical appearance. Sixty-three per cent in group
C had no germinal centres demonstrable com-
pared with 9% in groups A and B, and atrophy
of the thymus gland was seen more commonly
in those patients who failed to improve. The
majority of patients whose glands were only
slightly atrophic or contained numerous germi-
nal centres were young females. These results
would seem to agree with those of Mackay et al.
(1968) and are indicative of a better prognosis
after thymectomy for patients with thymic
hyperplasia.

Since the mean postoperative follow-up period
was longest in group A (Table 1) and the time
required to reach this state varied from six
months to 2½ years, it is possible that with further
observation the correlation between the histo-
logical findings and the clinical grouping may
have changed, although this is unlikely since the
number of patients in group B was small and
75% of patients in group C had died. To avoid
this discrepancy, a clinical and histological
assessment of patients was made nine months
after thymectomy (Fig. 2) but even during this
initial period 10 patients with germinal centre
hyperplasia had improved and only one had
deteriorated.

The possible contribution of pre- and post-
operative medication has been considered. Two
patients in groups A and B who had numerous
germinal centres received steroids postopera-
tively and on both occasions further clinical
improvement occurred. In one patient, steroids
were stopped and in another they were reduced
to a maintenance dose without any clinical de-
terioration. While the use of steroids appeared to
contribute to the overall postoperative improve-
ment of these two patients, it cannot be accepted
that their use was a major factor determining a
better prognosis in groups A and B as a whole
since they were used far more frequently but with
less benefit in group C. The administration of
steroids preoperatively and the incidence of
changes in postoperative anticholinesterase med-
ication did not differ significantly between groups
A and B and group C.

Two theories have been proposed to relate the
histological appearances of the thymus gland
with the pathophysiology of myasthenia gravis.
Goldstein (1966) has suggested that thymic
hyperplasia leads to the production of a neuro-
muscular blocking agent, while Alpert et al.
(1971) have advanced the concept of thymic
lymphocytes inducing neuromuscular damage.
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Both theories would be consistent with an improvement in myasthenic symptoms after thymectomy and it is conceivable that the degree of improvement would be proportional to the extent of germinal centre hyperplasia. However the information available is contradictory and the present communication simply increases the evidence in favour of such a correlation. The issue is of more than just theoretical interest because of its possible importance in the selection of patients for thymectomy and as a prognostic indicator.

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REFERENCES


