Actuarial analysis of the occurrence of remissions following thymectomy for myasthenia gravis in 400 patients

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Abstract
The role of thymectomy in the treatment of myasthenia gravis (MG) was analysed in 400 patients affected with generalised MG operated on between 1974–83, and prospectively followed up for five years after surgery. The occurrence of stable remission (SR) (that is, complete clinical drug-free remission that remains stable for all the subsequent follow up) was the endpoint of survival analyses and the distribution of SR time (SRT, that is, the interval from thymectomy to the occurrence of SR) was assessed by actuarial and Cox multivariate analyses. SRT distribution after surgery showed a slow progressive increase of cumulative SR rate that could both be ascribed to a delayed effect of thymectomy as well as reflect the natural history of MG, itself characterised by an increasing probability of spontaneous remission with time. SRT distribution was similar after stratification for all variables studied except when patients without thymoma were stratified for the need for immunosuppressive treatment in addition to thymectomy. Patients without thymoma who did not require additional immunosuppressive therapy (n = 130) had the highest SR rate occurring in the two years after thymectomy, and differed from patients treated with immunosuppressive drugs who showed the highest SR rate five years after surgery. Actuarial analysis has therefore identified a subgroup of patients where SR, occurring in the first years after surgery, is more likely to be ascribed to thymectomy than merely reflect the natural course of the disease.

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction in which the thymus gland seems to play an important pathogenetic role. Based on histological and immunological abnormalities of the myasthenic thymus, and on the excellent outcome reported in many series of surgically treated patients, thymectomy is now generally accepted as the mainstay of therapy of MG.

The effects of a therapeutic approach on the natural course of MG may be difficult to evaluate: after a few initial years of deterioration, the disease stabilises and often shows a spontaneous improvement with some probability of permanent clinical remission several years after onset. A complete clinical remission may also sometimes occur spontaneously during the first years of the disease, but in the case of generalised MG, it usually lasts a few months. Permanent remissions occurring in the years immediately after thymectomy may be more probably ascribed to surgery than those occurring several years later which may merely reflect the natural course of the disease. Our large series of generalised MG patients operated on by the same surgeon and with a postoperative follow up carried out by neurologists with a uniform method of assessment, offered a good opportunity for a detailed analysis of the chronological correlations between the occurrence of remissions and thymectomy.

Patients and methods
Between 1974–83 435 MG patients had thymectomy in the thoracic surgery division of our institution. Diagnosis was established according to clinical (history of fluctuating skeletal muscle weakness that worsened with repeated effort and improved with rest) and pharmacological (transient decrease of muscle weakness on injection of anticholinesterase drugs) criteria. The clinical status was assessed by objective measurement of the fatigability of different muscle groups with physical tests (such as horizontal holding of arms or legs, rising from a supine position, looking to one side or upwards, reading aloud) and of respiratory function. Patients were graded according to the classification of Osserman and Genkins.

Thymectomy was always performed by the same surgeon (GM). In all the patients without radiological evidence of a thymoma the surgical approach to the thymus was obtained through a cosmetic collar incision low in the neck, the inferior skin flap being raised and dissected from the sternum that was split for a length of 8–10 cm. A specially developed V-shaped sternal retractor with two non parallel branches was applied to separate the split bone allowing a wide exposure of the thymic bed. This partial median sternotomy allows a good visualisation of the two thymic lobes, both pleural surfaces, and the pericardium. All the fat between the two phrenic nerves was removed with the gland, an effort being made to remove all thymic tissue and suspicious looking fat of the anterior mediastinum.
When needed (especially in elderly or obese patients, or in the case of a thymoma) a total median sternotomy was performed.

Patients were prospectively followed up after thymectomy with at least one yearly visit for the first five years after surgery, and placed at the time of the visit in one of the following categories:
Remission: full working life with no restriction and no subjective myasthenic symptoms for at least six months without drug treatment. A small degree of permanent objective weakness, unrelied by neostigmine, is permitted.
Improved: no symptoms or signs but still on drug treatment, or still symptomatic but in a milder stage than before thymectomy.
Unchanged: minimal or equivocal changes.
Worsened: definitely worse than before surgery.
Postoperative death: postoperative complication (respiratory, cardiac or septic) occurring within 30 days from surgery.
Death from MG: if death occurred after a progressive clinical deterioration with respiratory distress and final respiratory failure and/or cardiac arrest.
Death not related to MG.

The decision to introduce immunosuppressive treatment in addition to thymectomy was made during follow up if the patient met one of the following prospectively defined criteria: a) definite worsening with severe bulbar symptoms (or respiratory insufficiency), unresponsiveness to increased doses of anticholinesterases, occurred after thymectomy; b) clinical status was unchanged two years after surgery; c) severe bulbar symptoms (or respiratory insufficiency) were present before surgery. Prednisone was the immunosuppressive drug of choice; azathioprine or cyclophosphamide being reserved for corticosteroid unresponsive patients (in this case, in addition to corticosteroids) or if there were contraindications to corticosteroids. Prednisone was given as a single daily dose, starting with 12.5 mg/day, slowly increased up to 100 mg/day in about 15-20 days. After a clinical improvement had occurred and remained stable for at least one month, prednisone was slowly tapered by 12.5 mg/week every other day, until 100 mg/0 mg on alternate days; then prednisone was tapered more slowly according to clinical status. Azathioprine was given at 2-4 mg/kg/day and cyclophosphamide at 1-2 mg/kg/day, individually maintained to adjust a white blood cell count around 4000 cell/mm³, duration of treatment depending on clinical status. Plasma exchange treatment was added to the immunosuppressive drugs only in case of respiratory insufficiency. Six to ten exchanges (according to clinical status) of a plasma volume equivalent to 5% of the patient's body weight were performed using an intermittent flow cell separator on alternate days. Human albumin solution, human immunoglobulin fractions, normal saline, and fresh frozen plasma were used as replacement fluids.

At the final assessment (winter 1988) patients were classified as stable remission (SR) if, once in remission, their clinical status had remained stable at all the subsequent follow up. Cases with the pure ocular form of the disease were not included in our analysis which is therefore based on 400 patients (105 in SR) affected with generalised MG with a disease duration longer than six and a postoperative follow up longer than five years. Patients were tabulated for each of the following variables considered of possible prognostic importance (table): a) disease onset and surgery (latency of surgery), b) maximal disease severity before surgery (severity of disease), c) age at onset, d) sex, e) disease duration (years), f) clinical status at time of last visit (remission, improved, unchanged or worsened), g) number of stable remissions (if any) before surgery and h) number of relapses.

### Table: Patient characteristics and clinical status after thymectomy

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Thymoma</th>
<th>No thymoma</th>
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<tr>
<td>Total</td>
<td>400(105)</td>
<td>100(12)</td>
<td>300(93)</td>
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<td>Latency of surgery</td>
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<td>&lt; 1 year</td>
<td>220(63)</td>
<td>69(9)</td>
<td>151(54)</td>
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<tr>
<td>&gt; 1 year</td>
<td>180(42)</td>
<td>31(3)</td>
<td>149(39)</td>
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<tr>
<td>Severity of disease*</td>
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<td></td>
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<tr>
<td>Mild (IIA)</td>
<td>109(36)</td>
<td>18(5)</td>
<td>91(31)</td>
</tr>
<tr>
<td>Severe (II, III, IV)</td>
<td>291(69)</td>
<td>82(7)</td>
<td>209(62)</td>
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<td>Age at onset</td>
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<tr>
<td>&lt; 30 years</td>
<td>201(72)</td>
<td>12(2)</td>
<td>189(70)</td>
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<tr>
<td>&gt; 30 years</td>
<td>199(33)</td>
<td>88(10)</td>
<td>111(23)</td>
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<tr>
<td>Immunosuppressive therapy in addition to thymectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not given</td>
<td>151(50)</td>
<td>21(3)</td>
<td>130(47)</td>
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<tr>
<td>Given</td>
<td>249(55)</td>
<td>79(9)</td>
<td>170(46)</td>
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<td>Corticosteroids alone</td>
<td>135(41)</td>
<td>26(4)</td>
<td>109(35)</td>
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<td>Corticosteroids with azathioprine</td>
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<td>Corticosteroids with cyclophosphamide</td>
<td>13(2)</td>
<td>7(1)</td>
<td>6(1)</td>
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<td>Azathioprine alone</td>
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<td>6(0)</td>
<td>11(4)</td>
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<td>Cyclophosphamide alone</td>
<td>5(1)</td>
<td>3(0)</td>
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<td>Plasma exchange in addition to immunosuppressive drug</td>
<td>33(2)</td>
<td>17(0)</td>
<td>16(2)</td>
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</table>

### Notes

*: number of stable remissions.

*: according to Oserman and Jenkins classification.
for different patient subgroups and their equality tested by computing the generalised Wilcoxon test. The influence of multiple variables on SRT distribution was estimated using the Cox proportional hazard model. Factors that had significant influence on the model were included stepwise. The significance of each factor was calculated by the maximum likelihood ratio. A p value of 0.1 was set to enter a variable in the model, while a p value of less than 0.05 was regarded as statistically significant. The data were processed with BMDP Statistical Software package (BMDP Statistical Software, University of California).

Results

Two hundred and ninety one women and 109 men were studied (table). The mean age at onset of the disease was 32.1 (range 15–70) in the women (where in most cases symptoms began in the second and third decade) and 36.4 (range 16–65) in men (onset of symptoms usually between 20–50 years). At the maximal deterioration before surgery the clinical grading was: 56% (222 patients) in stage IIB, 27% (109 patients) in IIA and 17% (69 patients) in III–IV. The mean time between disease onset and thymectomy was 2.5 years, with more than half the patients (55%) operated on within one year from onset. One hundred patients (25%) were affected with thymoma with a mean age at onset significantly higher than non-thymomatous cases (44.3 and 29.6, respectively) (p < 0.01) (Student's t test), while the clinical grading before surgery was similar in the two groups. Two hundred and forty nine patients (62%) required other immunosuppressive treatments in addition to thymectomy (table). Immunosuppressive therapy was started before surgery in 32% of these patients, within two years from surgery in 7%, and later in the remaining 61%.

At the final assessment (n = 388, death not related to MG excluded) (table) 27% patients were in SR, 57% were improved 11% unchanged or worse. Postoperative mortality was 2% and overall mortality related to MG 3%. Both mortality rates were significantly higher (p < 0.01) (Chi-squared test with Yates' adjustment for continuity) in the thymomatous patients.

The main factor significantly influencing the SRT distribution was the presence of thymoma both in unifactorial (p = 0.0003) and in multifactorial (p = 0.0003) analysis. Patients with thymoma had a lower SR rate than those without (12% vs 31%). In the presence of thymoma the occurrence of SR was not influenced by any of the variables studied.

In patients without thymoma the age at disease onset and the latency of surgery significantly influenced the SRT distribution. Patients younger than 30 at disease onset had a significantly shorter SRT (p = 0.01) than that of the older patients, and the mean age at disease onset of patients who achieved SR is lower than that of patients not in SR (26.5 vs 30.5). Chi-squared analysis showed that, with an age cut-off value of 30, the SR rate of patients grouped in five year classes was not significantly different within groups below or above the cut-off. On the contrary, patients above 30 had significantly lower SR rate (p < 0.01) than patients below 30. Patients operated within one year from disease onset had a significantly shorter SRT (p = 0.04) than that of patients operated on later. Patients treated with immunosuppressive therapy in addition to thymectomy had a significantly longer SRT as shown by both unifactorial (p < 0.005) and multifactorial analysis (p < 0.02). Maximal disease severity before surgery, time of onset of immunosuppressive treatment before or after thymectomy, different immunosuppressive regimes, sex, and number of germinal centres in the thymus did not influence SRT distribution.

The temporal pattern of the occurrence of SR after thymectomy

Patients without thymoma. The plot of the actuarial estimates of SRT distribution for the study population without thymoma shows that cumulative SR rate progressively increases with time after surgery (fig 1) but the slope of the curve is sharper (that is, the increase of the SR rate is more pronounced) between first and second and between fourth and fifth year of follow up. Stratification according to each of the following variables: latency of surgery, maximal disease severity before surgery, age at

Figure 1 Cumulative stable remission (SR) rates after thymectomy (actuarial estimates) in MG patients without thymoma. Each point represents the estimated SR rate for each year of follow up. SR rates are shown for all patients (□) (n = 300), and for patients treated with (▲) (n = 170) or without (●) (n = 130) immunosuppressive therapy in addition to thymectomy. The curves for the latter two subgroups of patients were significantly different (p = 0.0045).

Figure 2 Cumulative stable remission (SR) rates after thymectomy (actuarial estimates) in MG patients with thymoma. Each point represents the estimated SR rate for each year of follow up. SR rates are shown for all patients (□) (n = 100), and for patients treated with (▲) (n = 79) or without (●) (n = 21) immunosuppressive therapy in addition to thymectomy.
Actuarial analysis of the occurrence of remissions following thymectomy for myasthenia gravis in 400 patients

disease onset (with cut-off value of 30), sex, and number of germinial centres, yielded SRT distribution similar to that of the entire group of nonthymomatous patients. Conversely, stratification according to the need for immunosuppressive therapy in addition to thymectomy (since both the time of onset of immunosuppressive treatment before or after thymectomy and the different immunosuppressive regimes did not influence SRT distribution, all the patients that were administered immunosuppressive therapy were computed together) yielded two completely different curves (fig 1), showing only one sharp increase of the SR rate, each curve in a different point: between first and second year of follow up for patients without additional immunosuppressive therapy, and between fourth and fifth year of follow up for the others. These two curves are significantly different according to the generalised Wilcoxon test (p < 0.005).

Patients with thymoma. Actuarial analysis shows, in these patients, that cumulative SR rate progressively increases with time after surgery without abrupt slope changes (fig 2). Stratification according to each of the variables deemed of possible importance in the prognosis yielded temporal patterns of SR rate similar to that of the entire group of patients with thymoma and without significant differences between subgroups. Most (79%) of these patients required immunosuppressive treatments in addition to thymectomy and the plots of the actuarial curves of patients with or without additional immunosuppressive therapy did not significantly differ, again showing a slow progressive increase with time after surgery (fig 2), similarly to the entire group of patients with thymomatous MG.

Discussion

The outcome at the end of follow up
There is widespread consensus on the use of thymectomy in all adults with generalised MG.21-34 Due to the improvement in anaesthesia, surgical technique, and postoperative care, thymectomy is extremely safe. Operative death in nonthymomatous MG is rare,20 29 33 34 45 and the outcome seems excellent in the majority of reports.11-30 Analysis of these studies is, however, hampered by several biases: their retrospective nature, variability in the selection of patients or operative route, different concurrent medical therapy or clinical criteria of evaluation, limited number of patients or, to increase the number of cases, comparison of patients spread over a lengthy time interval (with changes in medical, surgical, and intensive care management). The efforts to compare retrospectively medical and surgical treatments yielded conflicting results,11-16 22 30 46 and a prospective randomised study, although advocated,15 46 47 has never been organised.

Overall stable remission in 27% of patients compares favourably with several other reports.11-16 22 30 46 Different remission rates may result from different selection criteria or surgical techniques or even from a different definition of remission. Lower remission rates (5-21%) are usually reported by studies where thymectomy is reserved for patients who failed to respond to medical treatment20 29 or when transcervical thymectomy,20 27 which may result in subtotal thymus removal,29 30-32 is used.

There seems to be a direct relationship between the extent of thymectomy and the highest remission rates (46-59%) were reported by studies which used the extended transternal thymectomy.18 24 28 29 'This suggests that the partial transternal approach used in this study did not always result in a total thymectomy. In addition the remission rate reported in our study may depend on the restrictive definition of stable remission which includes not only clinical and pharmacological criteria but also a prolonged temporal criterion.

On unifactorial and multifactorial analysis the presence of a thymoma was associated with a lower remission rate and a high mortality than in patients without thymoma. This agrees with all previous reports,12 14 16 17 20-25 29 30 33 35 37 38 46 indicating that in patients with thymoma MG is more severe and probably little influenced by thymectomy which is, however, necessary to remove the tumour.21 29 32 Unifactorial and multifactorial analyses indicated that, in patients with thymomatous MG, such a poor prognosis was unaffected by all the other variables studied.

In patients without thymoma the multifactorial analysis indicated that the occurrence of SR was significant for patients with or without thymoma, the need for immunosuppressive treatments in addition to thymectomy, and the age at disease onset. Patients who did not require additional immunosuppressive therapy and were operated on early in the course of the disease (that is, within one year from onset) had an SR rate of 44% compared with 26% of the others (p < 0.04) (Chi-squared test). An early thymectomy is advocated by most reports12 16 17 20 21 24 26 27 30 34-35 and probably prevents extra-thymic tissue developing autoimmune activity.41 46-47 In addition, a young age (below the age of 30) at disease onset further increased the SR rate—patients who did not require additional immunosuppressive treatment, who had early thymectomy and were below 30 years of age at disease onset had an SR rate of 59% compared with 26% of the others (p < 0.01) (Chi-squared test). The relationships between age at disease onset and outcome are controversial12 and most reports show no significant relationship between a young age at onset and a better outcome after thymectomy.12 16-18 21 27 28 Our analysis confirms that an age below 30 improves outcome only in patients without thymoma.30

The temporal pattern of the occurrence of SR after surgery
The clinical effectiveness of thymectomy may be reliably quantified in terms of occurrence of complete and sustained clinical and pharmacological remission,29 47 which represents a clear-cut objective change in the quality of the patient's life. Progressive increase of remission rate with the length of follow up (fig 1) agrees
with all previous reports, but cannot be simply interpreted as a delayed effect of thymectomy. The natural history of MG is itself characterized by an increasing probability of spontaneous remission with time. For this reason, in the absence of a concurrent control group of nonthymectomized patients, no definitive conclusions about the effectiveness of thymectomy can be drawn from a simple analysis.

Actuarial analysis is probably the best available statistical method to describe the chronological correlations between the occurrence of remission and thymectomy. In our study this analysis has shown that in patients without thymoma the temporal patterns of the occurrence of SR after surgery were significantly different in the groups with or without additional immunosuppressive therapy. Patients who required immunosuppressive treatments in addition to thymectomy displayed an SR rate progressively increasing with time after thymectomy with a late more pronounced increase between fourth and fifth year after surgery, while patients who were treated only with thymectomy and anticholinesterases showed an SR rate sharply increasing in the two years immediately after surgery and then showing only slight further increments (Fig 1).

Only the subgroup of patients without thymoma and whose response to thymectomy was good enough not to require further immunosuppressive treatment had such a peculiar increase of SR rate in the two years after surgery. Most (69%) of these patients in remission had been thymectomised within one year from disease onset, and therefore reached a stable remission in the first years of the course of the disease when maximum disease severity, crises, and even death are to be expected from the natural history of MG.

In conclusion, actuarial analysis of remission rate after surgery usually demonstrates a progressive increase with time that could both be the effect of thymectomy as well as reflect the natural history of the disease. In our analysis, stratification of data has identified a subgroup of patients without thymoma and who did not require immunosuppressive treatments in addition to thymectomy who had a number of early stable remissions significantly higher than other subgroups. Such early stable remissions are not predictable simply on the basis of the natural course of MG and, since they occurred in the years immediately after surgery, they are probably to be ascribed to thymectomy. Transcortical extended thymectomy, that is supposed to assure total thymus removal reliably, yields a high remission rate with usually most remissions occurring in the first two to three years after surgery, often without additional immunosuppressive treatments. Conversely, the plot of remission rate after cervical thymectomy, where total thymus removal is less probable, shows a slowly progressive increase after surgery that can be equally ascribed to thymectomy, additional immunosuppressive therapy, time alone, or all these factors.

In our series, where an effort was made to remove all thymic tissue with the surrounding fat, a subgroup of patients clearly stands out, in which thymectomy has probably yielded a high rate of early stable remission unexpected from the natural history of the disease. The reasons why early stable remission was less likely in the other patients may be subtotal thymus removal, delayed surgery, or other factors. Prospective immunological studies of phenotypic and functional properties of thymocytes and peripheral lymphocytes are in progress and may be useful to identify prognostic factors at the time of thymectomy.

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Actuarial analysis of the occurrence of remissions following thymectomy for myasthenia gravis in 400 patients

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