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Myasthenia gravis treatment: twelve years experience on 110 patients

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The clinical conditions of 110 patients affected by myasthenia gravis (MG) were followed from two to twelve years. Patients with thymectomy showed a statistically higher percentage of clinical remissions than patients without thymectomy. In patients without clinical remission immunosuppressive drugs were prescribed in different schedule; the greater percentage of pharmacological remissions with less adverse effects was obtained with administration of prednisone 50-75 mg/die initially, than gradually reduced to smaller dosage in alternate day, associated to azathioprine. Plasmapheresis, performed in six cases not responders to immunosuppressive drugs, always showed a positive and even prolonged effect.

Key-Words: Myasthenia Gravis – Themectomy – Steroid therapy – Immunosuppressive drugs – Azathioprine

Introduction

There have been significant advances during the past 15 years in research into the pathogenesis of myasthenia gravis (MG), which has been clearly identified as an autoimmune disease [5,6,10,11,31]. This has provided a sound rationale for immunosuppressive treatment such as thymectomy, steroids, azathioprine and plasmapheresis [2,12,27,32,33]. However, opinions differ regarding the value of thymectomy in the various stages of the disease and in relation to age and sex, and on the dosages of immunosuppressants, their timing sequence or combination [1,8,14,19,20,24,25,28,29]. There are probably not enough reports on large clinical series relevant to these points. We report the effects of several treatments observed in a population of 110 MG patients followed for 2 to 12 years with the purpose of collecting data to outline the most suitable therapeutic approach for the myasthenic patients. Therefore in this investigation we included all the common immunosuppressive procedures adopted up to now, even if with different physiopathologic mechanisms.

Patients and methods

We have considered 110 MG patients admitted to our department in the past 12 years: 49 males and 61 females with the age and sex distribution represented in *Figure 1*. The well-known predominance of young females and of older males is evident. 19 patients had thymoma (17.3%); their distribution is indicated by asterisks in the same figure.
Disease severity was assessed according to the Osserman classification on admission to our department (*Table I*). Most of the patients were examined and investigated at several intervals by us and all were followed up personally between August 1984 and April 1985.
Different groups of patients have been compared. Even if we could not randomize the cases of each group because of the retrospective setting up of the study, this feature tends to minimize the bias. Furthermore precise diagnostic criteria were observed for each group.
Clinical examination was conducted according to a checklist, including: presence/absence of ptosis, control of ocular motility, chewing, swallowing, speech, strength of eyelid closure, sucking,

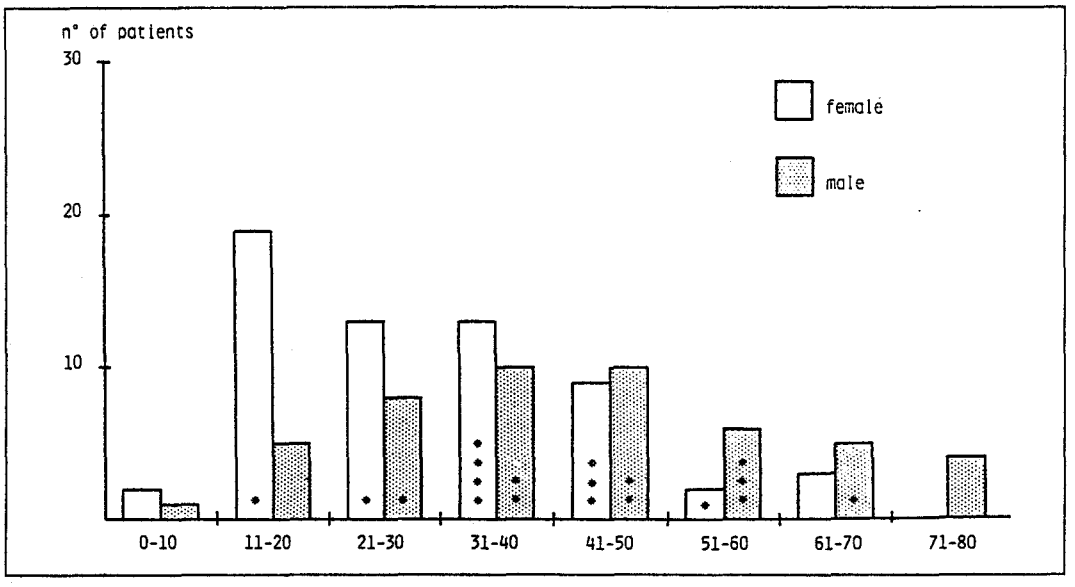

Fig. 1. *Distribution of the patients according to their sex and age at onset of M.G. Each asterisk signs one patient with thymoma.*

blowing; ability to keep the head lifted (at least 45° from the supine position for at least 30 sec.), arms raised and oustretched for at least 60 sec, and legs outstretched for at least 30 sec, grip strength, and number of times the patient could assume the squatting position.

EMG (including needle examination, repetitive nerve stimuation and, if necessary, single fiber EMG) was performed to support the diagnosis in every patient, and in almost all patients it was repeated more than once to check the evolution of the disease.

Patients off therapy for at least six months and without clinical signs or symptoms were classified as in clinical remission (CR). Most of the remaining patients were on immunosuppressive therapy, the aim be always to reduce or eliminate anticholinesterases as soon as patients were able to lead a fully independent life. Patients on immunosuppressive therapy without signs or symptoms of MG were classified as in pharmachological remission (PR). Those still dependent on anticholinesterases or with only mild MG and showing a definite increase of strenght in the affected muscles were classified as improved (I). Patients showing no noteworthy improvement were rated unchanged (U). In the case of patients listed as died, death was related to MG.

All our thymectomized patients have been operated on by transcervical and most by transternal approach.

69 patients were treated with immunosuppressants according to various schedules: A) prednisone over 80 mg daily (12 cases); B) prednisone 50-75 mg daily (14 cases); C) prednisone up to 50 mg daily (8 cases); D) prednisone as in A, plus azathioprine 100 mg daily (8 cases); E) prednisone as in B, plus azathioprine 100 mg daily (27 cases). Three patients were treated in the first two weeks with dexametazone 16 mg, corresponding to the highest dose of prednisone, and they have been included in group A. In all patients the dosage of steroids was gradually reduced to alternate day

TABLE I. *Patients classification*

Classification* at time of the first observation	Number of patients F	M
1	6	7
2a	17(1)	11
2b	25(6)	28(8)
3	12(2)	1
4	1(1)	2(1)
	61(10)	49(9)
Tot.	110 (19; 17.27%)	

* Osserman and Genkins, 1971, ( ) patients with thymoma

dosage and generally maintained at less than 30 mg on alternate days or, if possible, discontinued. Azathioprine was maintained at 100 mg daily as a rule, being reduced to 50 mg daily in only a few cases.
All the statistical evaluations were done with the ^{2} test.

Results

Our first aim was to determine the therapeutic effectiveness of thymectomy. We therefore compared the course of the disease in the patients who underwent thymectomy with that of those who did not, as shown in the histogram of *Fig. 2*. The clinical remission rate was much higher in the thymectomized than in the unthymectomized patients (24 out of 82 or 29,2% versus 2 out of 28 or 7,1%; $p < 0,05$). It is worth noting that unthymectomized patients in CR had ocular myasthenia. Unthymectomized patients responded well to immunosuppressive therapy.
Since the need for thymectomy in patients with thymoma is obvious, we evaluated the effect of the operation in patients without thymoma. In this population the complete remission rate was higher in the thymectomized patients (22 out of 63 or 34% versus 2 out of 28 or 7,1%; $p < 0,02$) but there were no substantial variations in the other groups (*Fig. 3*).
Since some authors are in favor of thymectomy in patients without thymoma not over the age of 40 (9,22), we compared the clinical course of thymectomized patients up to the age of 40 (A) and over 40 (B) with that of unthymectomized patients in the same age groups (*Fig. 4*). The younger patients who had undergone thymectomy showed a further slight rise in clinical remission rate (18 cases out of 48 or 37,5%). The histogram of the thymectomized patients over 40 also shows a high CR rate (4 cases out of 15 or 26,6%). However mortality too was higher (4 cases or 26,6%).
Finally we compared the course of the disease in patients with ocular myasthenia who underwent thymectomy with the same class of patients who did not, and here again the clinical remission rate was higher in the patients treated surgically (*Table II*).
The last question about thymectomy was to assess its influence on the course of the disease according to the interval between onset of MG and surgery. 56 patients underwent surgery within 2 years of onset and 26 after a long interval. In the first group 20 were in CR and 19 in PR compared with 4 in CR and 5 in PR among the patients in whom thymectomy was delayed. The difference in clinical remission rate between the two groups was significant ($p = 0,05$) and the difference in clinical and pharmacological remission rates combined, highly significant ($p < 0,01$).
In the group of 69 patients treated with immuno-

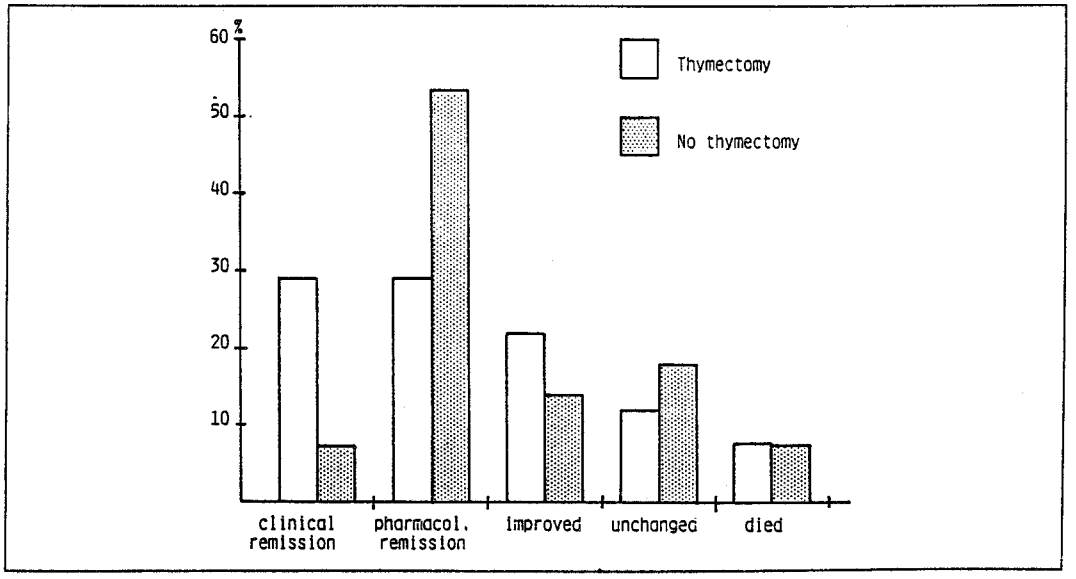

Fig. 2. *Follow up of myasthenic patients. Comparison between the patients who underwent thymectomy and the ones who did not. Clinical remissions are significantly more frequent in patients with thymectomy ($p < 0.05$).*

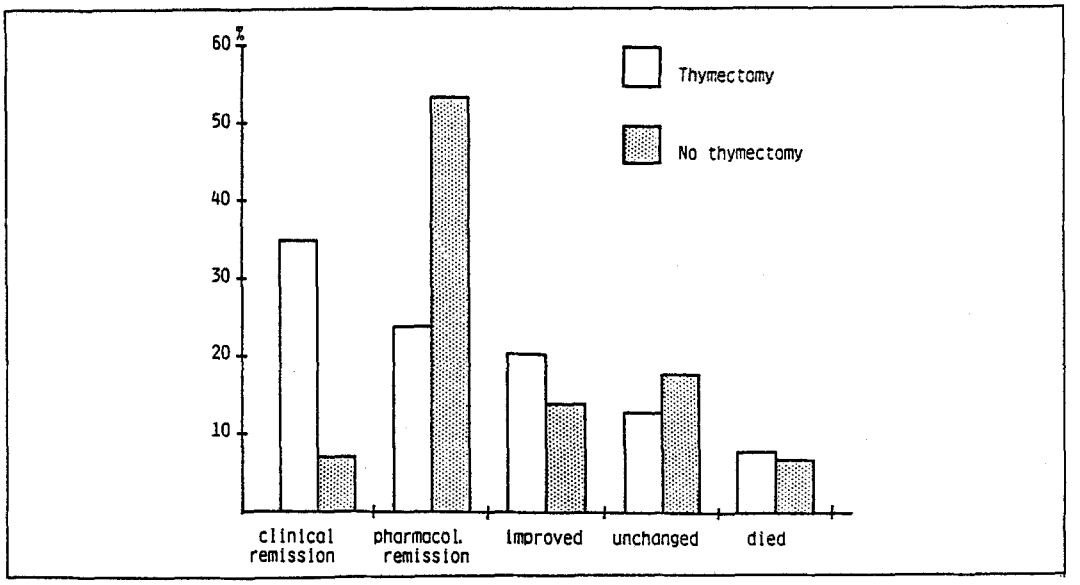

Fig. 3. *Follow up of myasthenic patients without thymoma. Comparison between the patients who underwent thymectomy and the ones ones who did not. Clinical remissions are significantly more frequent in patients with thymectomy. ($p < 0.02$).*

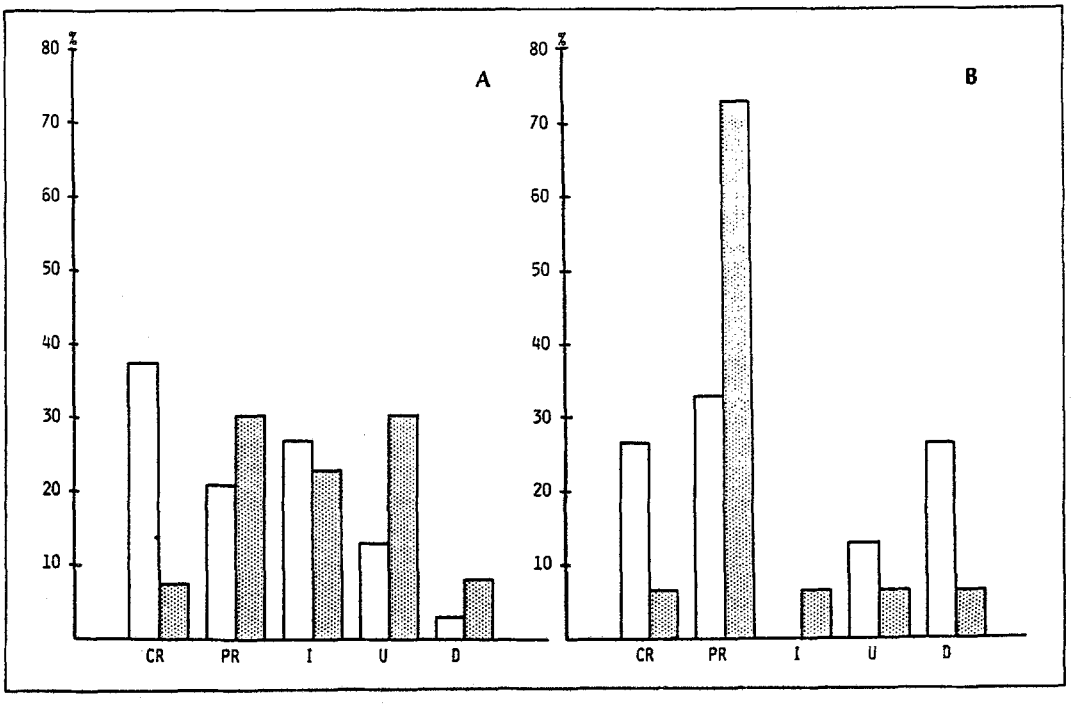

Fig. 4. *Follow up of myasthenic patients, 40 years old or younger (A), and over 40 years (B), without thymoma. Comparison between the patients who underwent thymectomy and the ones who did not thymectomy.*

TABLE II. *Clinical remission rate in patients with ocular myasthenia with and without thymectomy*

Number of patients with thymectomy	Clinical remission
5 (2M 3F)	3 (60%) (1M 2F)
without thymectomy	
8 (5M 3F)	2 (25%) (1M 1F)

suppressive therapy the benefit of treatment was confirmed by the high PR rate both among the thymectomized and the unthymectomized patients (see Table III). 6 patients who had been thymectomized and one who had not were weaned off immunosuppressants to achieve clinical remission. Side effects were not severe and not very frequent (*Table IV*). Correlation by treatment schedule (*Table III*) revealed a higher PR rate and a lower frequency of side effects in patients treated with the association of steroids in medium-dose (attack) and azathioprine (*Fig. 6*).

Plasmaexchange was performed in 6 cases of severe MG. This measure proved invaluable in all cases as support for immunosuppressants and to hasten the response. In one of these patients, who had necrosis of the femoral head, we were obliged to reduce the dose of steroid drastically; the condition improved greatly with courses of plasmapheresis at progressively longer intervals (from 1 to 3 months), and now 5 months after the last course the patient is little troubled by MG.

Discussion

Our practice has been to prescribe anticholinesterases, usually to start with, while waiting for other therapeutic procedures to take effect. Anticholinesterases have only symptomatic effects and they are not recommended for long term use, since they may impair neuromuscular function and impede control of the immunopressants action [4,16]. Management of the myasthenic patient should be directed to control the underlying immunological alterations.

Among the different comparisons taken into consideration, only a few have a statistical support. Thymectomy seems to be the first problem in the management of the myasthenic patients: it is mandatory in patients with thymoma, and is generally considered beneficial in MG patients without thymoma [17,19,26]. Our thymectomized patients show a significant higher rate of CR. It does not seem to be contraddictory that in the group of the thymectomized and the unthymectomized patients CR and PR together are not statistically different, since only CR is the real goal of the patient's management; maintaining the patient on

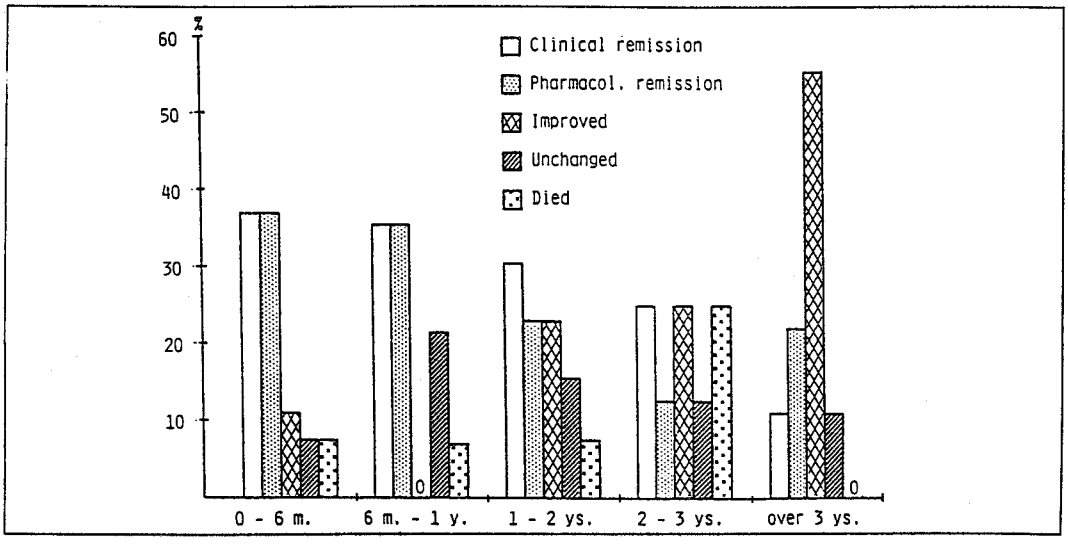

Fig. 5. *Myasthenic patients who underwent thymectomy. Clinical state in relation to the time between the onset of M.G. and thymectomy. There is a significant increase of remissions in patients with an interval shorter than 2 years in comparison to the others. ($p < 0.01$)*

TABLE III. *Effect of different programs of immunosuppressive therapy in myasthenic patients*

Dosage in the first weeks	Clinical remission	Pharmacol. remission	Improved	Unchanged	Died
A) Prednisone equal or over 80 mg/die	1	4	2	2	3
B) Prednisone between 50-75 mg/die	1	8	2	2	1
C) Prednisone equal or under 50 mg/die	2	2	1	2	1
D) Prednisone equal or over 80 mg/die + Azathioprine 100 mg/die	0	3	4	1	0
E) Prednisone between 50-75 mg/die + Azathioprine 100 mg/die	2	17	3	4	1

TABLE IV. *Side effects of immunosuppressive therapy in myasthenic patients*

Side effect	No. of patients in each therapeutic program					Total no. of patients
	A	B	C	D	E	
Steroids						
Weight gain	1	1	1	-	-	3 (4.3%)
Cushingoid appearance	2	1	-	-	-	3 (4.3%)
Gastritis	1	2	-	1	-	4 (5.8%)
Gastric ulcer	-	1	-	-	1	2 (2.9%)
Osteonecrosis	-	-	-	1	-	1 (1.4%)
Hypercholesterolemia	-	1	-	-	-	1 (1.4%)
Azathioprine						
Dyspepsia	-	-	-	1	-	1 (1.4%)
					Total	15 (21.7%)

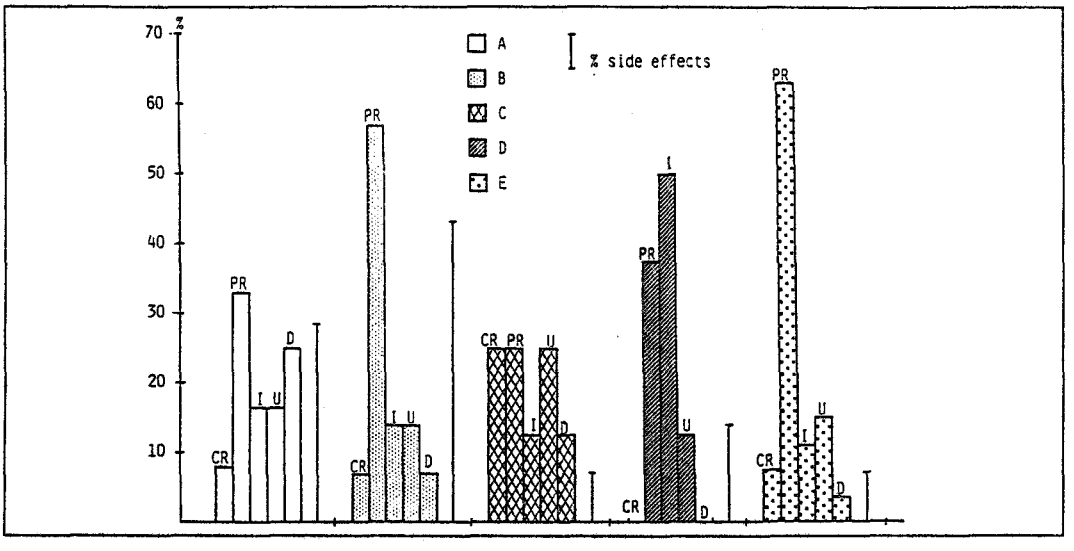

Fig. 6. *Follow up of myasthenic patients. Clinical state in relation to different therapeutic programs.*

immunosuppressants, with the risk of various side effects, is only an half success.

Like others [7,13,19], we have found that the earlier thymectomy is performed, the more effective it is and the comparison is highly significant. It therefore does not seem rational to give immunosuppressants first and leave thymectomy as a second-line treatment; indeed, patients treated in this way [20] show a lower CR rate and much worse side effects than in our series. The steroid-first approach is advisable only in debilitated patients to get them fit for surgery.

After the discussion of the statistical data, we think it worthwhile to consider other trends pointed out by our study. In patients over the age of 40 the thymectomy does not seem to be favorable, because of the high mortality, but this might have been lower, had these patients, seen in the first years of our experience, been treated previously with steroids and plasmapheresis. Thymectomy was rapidly followed by clinical remission even in two of our older than 40 myasthenic patients who had a long history of disabling disease. Our opinion is shared by many other workers [13,18,25,26,30].

Thymectomy is advisable even in patients with ocular myasthenia only. Its beneficial effects have recently been observed in 16 out 18 such patients [29].

In older patients surgical treatment should obviously be considered with caution, partly because older patients usually respond well to immunosuppressants [19] and partly because of the higher operative risk. We consider that thymectomy can be delayed or avoided altogether in cases of mild ocular myasthenia but we recommend it in cases of continuous diplopia.

The great majority of our patients who underwent thymectomy showed beneficial effects within the first year. In patients who are not in CR or not improving markedly within a year, immunosuppressants have to be considered. In such cases we gave prednisone 50 mg or more daily; exacerbation of weakness was, as a rule, slight or moderate in the first two weeks, only a few patients requiring transfer to intensive care. Within a few weeks the first signs of improvement were evident. The dose of steroid was gradually reduced and then given only on alternate days; in a few cases steroid therapy was eventually discontinued.

Patients responding poorly to immunosuppressants, even to high-dose steroids, were put on plasma exchange at lengthening intervals as prescribed by Rodwitsky et al. [23]. This procedure prevented or at least limited the adverse reactions that always attend administration of high-dose prednisone for several months.

In conclusion, the management of MG has become easier. Thymectomy is indicated in all patients except those with very mild symptoms or in very poor general condition. The operation should be performed one year after diagnosis to allow for spontaneous remission. If this does not occur within the year, the operation should then be performed as soon as possible. In cases of mild or moderate disease a year should elapse from thymectomy before immunosuppressive treatment is started to see whether clinical remission occurs; during this period anticholinesterase support may be given. Only if the patient still needs anticholinesterases beyond the year should prednisone plus azathioprine be considered, with the aim of obtaining pharmacological remission with the minimum of side effects. Rather than increasing the doses of steroid and/or azathioprine, we recommend plasmapheresis at lengthening intervals, since this combined with immunosuppressants have ensured substantial and lasting improvement even in the most severe or refractory cases [3,15,23].

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Sommario

Centodieci pazienti affetti da miastenia grave sono stati sottoposti a controlli clinici ripetuti lungo un periodo variabile da 2 a 12 anni. I pazienti operati di timectomia hanno presentato una percentuale di remissioni cliniche significativamente più elevata rispetto i pazienti non timectomizzati. La grande maggioranza dei pazienti che non hanno manifestato una remissione completa della sintomatologia clinica sono stati sottoposti a diversi programmi di terapia immunosuppressiva. La maggior percentuale di remissioni farmacologiche con minori effetti collaterali fu ottenuta con la somministrazione di una dose iniziale di prednisone di 50-75 mg/die, gradualmente ridotta nelle settimane successive ed infine somministrata a dì alterni, a cui veniva associata, dopo qualche settimana, azatioprina 1-2 mg/Kg/die. La plasmaferesi, eseguita su alcuni pazienti gravemente affetti dalla malattia, e che non rispondevano adeguatamente alle terapie farmacologiche, ha sempre manifestato un effetto positivo, e se ripetuta più volte nello stesso soggetto, anche durevole.

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