Ital. J. Neurol. Sci. 4: 399-407, 1983

Thymectomy in myasthenia gravis A review

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The role of thymectomy in the management of myasthenia gravis is reviewed in the light of the published data and of a personal series. The patients in whom the operation is most successful are non thymomatous patients aged between 10 and 40 years with an MG history of less than 3 years. There is no sex prevalence. Lasting improvement may be expected. There are no proven correlations between biological indices like the germinal centers in the thymus and/or AChR antibody titers and the postoperative course of the disease. Complete removal of the thymus seems to be crucial and hence the transsternal approach is preferred. The operation, less effective in patients with thymona than in those with an active thymus, is nonetheless necessary to in these patients prevent putative damage to surrounding organs from thymona infiltration. Why thymectomy should be effective in patients with an active thymus and not in those with a thymona may be revealed by in vitro studies of the interactions between thymic cells and peripheral B cells, now in progress.

Key-Words: Thymectomy — myasthenia gravis

1. Introduction

Since the first description of myasthenia gravis (MG) as a disease entity it was soon noticed that tumours of the thymus occurred more frequently in MG-patients than could be expected reasonably [86]. In large series of patients with MG thymomas are reported in 9-16% [60]. In patients with thymomas MG was present or developed subsequently in about 30-40% [51]. In 1936 Blalok [6] removed a thymoma in a 20 year old woman, who had suffered from increasingly severe periods of MG since the age of 16. In the last exacerbation her life was saved by prostigmin and artificial respiration. She recovered substantially in a few months. At the time of the report, 3 years later, she was in an almost complete remission. The relationship between the removal of the thymoma and the cure of the MG was so striking, that in 1941 Blalock decided "that it might be worthwhile to test the effect of total thymectomy in patients without demonstrable tumours" [7].The results in his 20 patients, of whom 2 had tumours, were that 3 patients were cured, 5 improved considerably, 3 did not improve and 4 died, 3 postoperatively and one after 8 months. Although the decision to remove the "normal" thymus seems illogical, the rationale was supported by the finding that 7 out of 10 thymuses showed an abnormal histological pattern, e.g. the presence of lymphoid follicles [85]. Blalock's initiative was carried on by Keynes, who performed 281 thymectomies between 1942 and 1956 [34]. The results were good in young patients (> 30 years) without thymomas, of whom one third went into a remission and one third improved considerably. In patients with thymomas however the results were equivocal [32, 79]. Keynes' results were at first not confirmed [14] but separation of the thymoma and non thymoma cases resulted in the same conclusions [15, 22, 90]. The evaluation of the results was hampered by methodological difficulties as prospective controlled studies have been carried out. The main doubt about the real effect of thymectomy concerns the chance that spontaneous improvement or even remission might occur as the natural course of the disease, which could be falsely interpreted as the effect of the operation. Other questions are: is

the effect of thymectomy dependent on the age and sex of the patient, on the duration and severity of the disease and on the presence of a thymoma? Finally, the role of the thymus in the pathophysiology of MG is still a matter of debate.

2. Thymectomy in patients without thymoma

The general consensus that thymectomy benefits the majority of patients without a thymoma has gradually evolved from a large experience in many centres all over the world. Although no prospective, randomized trials comparing operated and medically treated patients have been reported, at least 4 large series can be found in which thymectomized patients were compared with more or less matched controls, treated by the same doctors in the same periods [9,15,57,90]. In 4 other series [16,67,77,79] the medically treated "controls" were described as less severely affected than the operated patients. In all series the results in the thymectomized groups were better, even if only hard criteria such as remission or death are taken into consideration. Complete remissions varied from 18 to 38% (m = 28%) in thymectomized groups compared with 7.5-24% (m = 13%) in the patients treated with anticholinesterases. Death rates due to MG varied from 4.5 to 19% (m = 13%)in thymectomized groups and 15 to 42.5% (m = 22%) in the medical "controls". Remission or improvement was reported in 62 to 86% (m = 72%) and 24 to 55% (m = 41%) in the operated and medical series respectively.

The criteria for improvement however vary widely and usually include the reduction of anticholinesterases, which may be not very reliable. Another point of concern is the difference in the duration of the follow-up, which varied from one [90] to about 20 years [9]. This difference is important since the improvement is deemed to proceed up to 10 years after thymectomy. [66] From these and other large series of thymectomies [33,38,56,63,79,87] the following factors emerge which seem to influence the effect of the operation:

1. The best results may be expected in patients in the age groups 10-40 years with a duration of MG shorter than 3 years. Complete remissions after 1 year were reported in 8% [20] or 18% [56], after 3 years in 17% [20] or 25% [56,84] and after 5 years in 36% [20].

It is not clear whether operation in the first year after onset yields better results than operation in the second and third year [13,56], but in one study [65] the remission rate was higher if the duration of MG was shorter than one year. In fact most thymectomies are being performed after the first year of illness, as a certain time elapses in most patients before the diagnosis is made, particularly in mild and moderate cases. This delay of one or two years does not seem to influence the final outcome and avoids an operation in 2% of the patients who will have only one period of MG in their life with a complete spontaneous remission thereafter [58].

2. Men have about the same chance to improve as women [9,16,38,56,62,67]. Only in two series [37,50] better results were found in women, and in one series more complete remission occurred in men [87].

3. The rate of improvement does not seem related to the severity of the condition shortly before the operation [56,65], but in one series the remission rate was lower in the more severely ill patients [50].

4. Improvement may start on the day of the operation and exceptionally be complete after a few weeks (personal observations). In about 10% of my patients there was a short improvement during 2-6 weeks after thymectomy, with a return to the preoperative level. Although this fact is widely known (8,80, personal communications) and documented in an EMG-study [4]; no systematic clinical studies have been reported. It is my impression that this short improvement has no prognostic value in relation to the final outcome of the operation.

5. Long-term improvement is thought to go on for 7-10 years. [57,62,67], or at least 3-5 years [87] after thymectomy. In my series no further improvement seemed to occur later than 5 years after thymectomy [57]. Even if MG is not completely cured, the disease is usually quieted and has lost its umpredictable ups and downs, and the patient's condition is less influenced by infections and emotions [75]. Late exacerbations (e.g. more than 7 years after onset) and crises occurred much less frequently in thymectomized patients than in controls [58]. The effect of thymectomy appears to be permanent in most patients (33, 69, own observations) and no relapses have been reported in patients who reached a complete remission after thymectomy.

6. Children between 1 and 10 years are usually not subjected to thymectomy. In a search of the literature 33 cases were found with generalized MG [5,19,23,25,73], who underwent thymectomy. They were sometimes included in larger series with adults [33] or in reports on children up to the age of 16 [71,77]. Among these children remission was reported in 11, amelioration in 11, no effect in 2, death in 5, no follow-up in 4. These data suggest that the results are the same as in adults. However no control series matched for severity are available. In my series 3 of 8 patients with acquired, generalized MG went

into a spontaneous remission and 4 ameliorated considerably, all without thymectomy.
Juveniles (ages 10 to 16) seem to react as well as adults do (18,33 own findings), but in one study no difference in outcome between thymectomy and medical treatment was found [48].
Patients with congenital MG should be excluded from thymectomy since their disease probably has no immunological basis [91].
7. Patients with purely ocular MG have been excluded from thymectomy in most series, but they are included in some [36,79,87]. It is not evident why thymectomy does not seem to benefit patients with ocular MG but there are no convincing data to prove the contrary. Ocular MG is relatively rare in patients under the age of 40, which is a reason why no comparative studies have been reported.
8. The data on patients of over 45 years are contradictory. The result of thymectomy has not usually been stated explicitly in this category, if they were included in larger series in which most patients were under that age. The indication for thymectomy was gradually extended from 45 years [79], to 55 [69] or to 60 years [29, 52, 61, 81] or even higher ages [47, 52, 82]. In a recent series [52] 9 remissions and 3 improvements were reported in 12 patients from 55 to 74 years. Five of these patients had an atrophic thymus, 3 had hyperplasia, one a normal thymus and 3 a thymoma. These findings are different from those obtained in autopsies of 20 MG-patients of 60 years and older, in 11 of whom no thymus was found and only microscpic remnants in 9 [68], and lead to the conclusion that no rationale exists to perform thymectomy in patients over the age of 60. Since the thymus undergoes rapid involution with stress, it may be that the findings at autopsy are not representative for the situation in living patients.
In my own experience, although scanty, thymectomy in patients over the age of 50 had no effect, while on the other hand the spontaneous evolution in these patients (without thymomas!) was rather benign. Without controlled series the indication for thymectomy in patients over the age of 50 without thymomas remains to be proven.
9. Another point of contradiction is the relationship between the presence and abundance of germinal centres (lymph follicles) in the thymus and the effect of thymectomy. Some authors [20, 67] have stated that the early remissions were related to an absence of germinal centres, although the final outcome was not different [67]. Others did not find any correlation [8, 16, 56, 87] and in one series survival tended to be worse if the thymus was atrophic. [9]. It should be emphasized that hyperplasia or hypertrophy means that the medulla of the thymus is larger than the cortex, while the total weights of the thymuses removed at operation fall within the range of normality (10, own observations). Germinal centres are always situated in the medulla, although probably separated from it by a continuous epithelial layer with its associated basal lamina [41]. Some germinal centres may be seen in a thymus which is mainly replaced by fat, and in this respect classified as atrophic.
10. The titers of antibodies to acetylcholine receptor (anti-AChR) are usually high in patients under the age of 40 without thymoma [42] and fall after thymectomy if the patient improves [59], although they remain demonstrable even if a complete clinical remission is reached [59]. It is not known whether thymectomy will improve a patient with generalized MG without anti-AChR. These patients were rare in my series and always had a mild MG (the reverse is not true: patients with a mild MG may have high titers of anti-AChR [42]. The absolute value of the anti-AChR titer however is no indication for the effect of thymectomy.
11. Thymectomy fails to improve about 20% of patients under the age of 40 without a thymoma. It has been suggested that this failure is due to the incomplete removal of the thymus [26, 28, 30, 45, 72] there being aberrant thymus present either in the neck or in microscopic remnants scattered in the mediastinal fat [39]. A recurrence of myasthenia after an initially successful thymectomy has been reported also [26, 30, 45], which might be explained by an outgrowth of the aberrant thymus tissue. However the scarcity of these reports suggests that this is rather an exception than the rule.
These data are used in the discussion on the preference of cervical versus transsternal thymectomy. Advocates of the cervical approach to the thymus [35, 36, 65, 64] argue that this procedure is much more comfortable for the patient, with a shorter and less eventful post-operative course than thymectomy by sternal splitting, and with the same results, if the duration of the disease and the abundance of germinal centres in the thymus were taken into account [65]. Several recent reports [27, 43, 45, 46] however indicate that the results of thymectomy by transcervical route are not as good as those by sternal splitting. In one of these series [27], 7 patients who had not improved after transcervical thymectomy were reoperated transsternally. A mean weight of 23 gram thymus tissue was removed and 6 out of 7 patients improved subsequently.
Since the thymus must be considered a causative factor in the pathogenesis of MG, it is sound clinical reasoning that thymectomy should be as complete as possible. Therefore a transsternal approach combined with cervical exposure was

advocated to remove the aberrant tissue in the neck [28] while others [43] lay emphasis on the complete removal of the mediastinal fat. Since certain thymus dependent factors in the serum decrease sharply after thymectomy [92], these might be used to indicate the completenes of thymectomy. However, no relationship was found between the decrease of this serum factor and the effect of thymectomy in a series of 20 patients [92], but in this series no anatomical verification of the completeness of thymectomy was performed.

3. Thymectomy in patients with a thymoma

Thymomas are defined as primary epithelial tumours of the thymus, with or without a lymphocytic component [70]. Many classifications of thymomas have been proposed on the basis of a variety of microscopic or histogenetic criteria, but all subdivisions were felt to be artificial [70]. Other tumours of the thymus such as thymolipoma, carcinoid, seminoma, lymphocarcinoma and localized Hodgkin disease are not related to MG. Most authors [3, 24, 40, 44, 70] agree that no specific anatomical or histological features can be used to distinguish thymomas in MG from those without MG; only the spindle-epithelial type would be very rare in MG [11]. The histological picture bears no relation to the severity of the MG, but in general patients with a thymoma have a more severe MG. In my patients ventilatory insufficiency occurred in 52% of thymoma patients and in 14% of non-thymoma patients with generalized MG [57].
The effect of thymomectomy on MG is difficult to assess. In older series [25, 79] there was a high mortality (51-61%) either post-operatively or in the early course of the disease, but also in series started after 1960 [8, 16, 50, 78, 87] Mortality varied between 20 and 28%.
Complete remissions in these series varied from 10-20% but no comparison was made with medically treated controls. In all these series the improvement categories have lower percentages than in comparable series of thymectomies without thymomas reported by the same authors.
The difficulties in assessing the outcome of management of thymoma patients can be seen in the review of my own patients, followed in the period 1960-1982 (table I). Treatment with ACTH has commonly been used since 1965, prednisone since 1972, azathioprine from 1974. A minority of them apparently had a benign course, either with or without operation. Most patients however had to be treated with prednisone and appeared to be dependent on this drug as their condition deteriorated when prednisone was tapered off beyond a certain dosage. The effect of the operation therefore remains uncertain but cannot be very impressive.
The main reason to remove a thymoma is the potential invasiveness, which materializes in about one third of the patients. As far as invasive growth is reported in MG, about the same figures are given [60], which is remarkable as thymomas in MG are probably detected earlier and have a lower weight [70]. This leads to the supposition that invasiveness is a primary feature of

TABLE I.

MG with thymoma Follow-up > 3 yrs (60)		
	operation 50 patients	**no operation 21 patients**
Remission	3	3
Much improved	6	–
Improved	2	–
No change, alive	7 (a)	6 (b)
Deteriorated	6 (c)	1
Died from MG	11 (d)	8 (e)
Died from thymoma	3 (f)	1 (g)
Unclear, prednisone	12 (h)	–
Died from pancytopenia	–	2 (i)

a. 4 patients treated with prednisone of whom 3 improved
b. 2 patients received radiation of the thymoma
c. 3 patients treated with prednisone of whom 1 improved
d. no prednisone used (period before 1965)
e. 2 patients received radiation of the thymoma
f. recurrence of thymoma combined with exacerbation of MG
g. severe MG in remission with prednisone and azathioprine
h. 2 in remission, 3 much improved, 7 improved
i. MG much improved without therapy

the tumour and not related to its age. This was also suggested by the findings in my own patients where no relation was found between the invasiveness and the appearance on X-rays or CT-scan or with the duration of the clinical signs of MG. Even in patients with recent signs of MG the thymoma could grow invasively, while in others it remained encapsulated, without increase in volume on X-rays for many years.

A confusing aspect is the development of MG after removal of a thymoma. According to an extensive review of the literature [51] 33 patients who acquired MG in a period of 2 weeks to 6 years (mean 1.5 year), even of 22 years [40], after total removal of a thymoma and of the adjacent thymus have been reported. Since most of the patients whose mediastinum was later reexplored had no residual thymic tissue, it is likely that in the majority of the patients thymic tissue was absent when MG appeared. These data suggest that the onset of MG occurs in about 2% of the patients after removal of a thymoma. In my own series the detection of a thymoma preceded clinical MG in 5 of 71 patients. In my experience it is not uncommon for a thymoma detected at the onset of MG to have been seen on previous X-rays. As most thymomas are slowly growing tumours it is likely that a thymoma detected in the first year of MG has preceded the clinical signs. It seems largely a matter of chance whether a thymoma is detected and removed before or after the clinical signs of MG have been recognized. Thymomectomy does not prevent the appearance of MG, which accords with the rather poor result of this operation when MG has manifested clinically. This implies that thymomectomy should not be done as an emergency treatment in patients with severe MG. In older patients (over the age of 65-70 years) an expectant approach seems reasonable if a substantial tumour growth cannot be demonstrated and local tumour signs are not present.

In cases of invasive growth and incomplete resection of the tumour and/or with pleural metastases, radiotherapy (4500-6000 rads over 4-6 weeks) is usually recommended [3, 8, 24, 44, 76], with or without high dosage prednisone [21]. The indication for routine radiotherapy after macroscopically complete resection is controversial [2, 3, 44, 84]. In one series [44] 3 out of 47 patients who received radiotherapy later developed a recurrence and so did 3 out of 21 patients who were not irradiated. The possibility of serious side effects due to high dose mediastinal irradiation [83] e.g. oesophagitis, lung fibrosis, thyroid cancer, and myelopathy make this indication very dubious. Even in patients with incomplete removal, the use of radiotherapy should be subjected to critical studies since concomitant immunosuppressive drugs will also impede tumour growth, which in itself is often slow and cannot be estimated at the moment of operation.

It has been stated that even older patients should be subjected to thymectomy since a large percentage of them harbour hidden thymoma [84]. Although it is true that the prevalence of thymoma is much higher over the age of 40 (26.6% in my series [60], versus 8.2% under that age), the most reliable and economical (in costs and comfort for the patient) screening test is that of the anti-striated-muscle antibodies in the serum. If these are absent a thymoma is very unlikely [42, 53] and a CT-scanning of the mediastinum may be avoided.

Discussion

The beneficial effect of thymectomy on the natural course of MG in about 80% of the patients under the age of 40-50 years is well established but poorly understood. Improvement usually ensues gradually in one to three years after the operation or even after a longer period. Statistically the best results occur if thymectomy is performed in the first 3 years after onset, but it is impossible to predict the effect in the individual patient, even if the histological picture of the thymus is taken into account.

The long delay of the effect of thymoctomy is commonly explained by the time that is needed for the deletion of extra-thymic sensitized T-cells, which are supposed to enhance the autoimmune response. It is hypothesized that the thymus exerts its influence by humoral factors, "thymic hormones", the concentration of which steadily decreases after the age of 25 [1, 92] and sharply after thymectomy [89, 92]. In addition the thymus itself might be the source of the antigen i.e. the acetylcholine receptor protein, to which the autoimmune response is directed and which is probably situated in the myoid cells [31].

In MG thymuses the medulla harbours an increased number of large non-lymphoid interdigitating cells which are concerned in antigen presentation and stimulation of immune response [88]. In this way MG without thymoma would occupy a unique place in the spectrum of autoimmune diseases, which in general do not seem to respond favourably to thymectomy, although exceptions have been reported [49].

Although the size of the still active thymus varies widely in individuals of the same age, some data are in favour of the assumption that the thymus in MG patients remains more active and is more slowly replaced by fat [55]. This may be secondary to an immunological reaction inside the

TABLE II.

Characteristics of MG patients with and without thymoma		
	without thymoma (85%)	**with thymoma (15%)**
Age at onset of MG (60)	54% < 30 y.	85% > 30 y.
Male/female ratio (60)	4 : 6	1 : 2
Male/female ratio if onset between 10-40 y. (60)	1 : 4	3 : 5
Incidence of MG-crisis (57)	± 15%	± 50%
Only ocular MG after 3 years (60)	10%	0%
HLA-antigens (11,16)	B8 and DwR3 (<30 y.) B7 and DwR2 (>30 y.)	no preference
Anti-striated-muscle antibodies (42)	20% (low titers)	95% (high titers)
Other autoimmune diseases (57)	11%	27%
Lymphocellular infiltrates in muscle (55)	rare	frequent
Reaction to thymectomy	favourable	absent
Reaction to prednisone and immuno-suppressive drugs	variable	favourable

thymus itself, giving rise to germinal centres. These data are rather insufficient to explain the pathophysiology of MG originating in older age with a minimum of functioning thymus tissue, or in patients with thymomas without residual thymus.

Several characteristics distinguish patients without thymomas from patients with thymomas (table II), but it should be emphasized that some of them are statistical data that are not all applicable to the individual patient. The pathogenesis of the disease may be different in either category, but the "final common path", i.e. the damage to the acetylcholine receptors at the postsynaptic membrane mediated by, or at least concomitant with, anti-acetylcholine receptor antibodies, is probably the same. In patients with thymomas features of a more generalized autoimmunity (auto-antibodies, other autoimmune diseases, lymphorrhagic infiltrates in muscle [54]) are more abundant and the MG is more severe [57]. This may be due to a deficient immunoresponse (suppressor cell hypoactivity) connected with higher age and a difference in genetic factors (HLA-antigens). Since thymic abnormalities must precede clinical manifestation of MG, both germinal centres and tumour growth might be the result of the primary autoimmune process, rather than the cause of it. Why thymectomy is effective in patients with an "active" thymus and not in patients with a thymoma may be revealed by in vitro studies of the interactions between thymic cells and peripheral B-cells, which are now in progress [74, ...].

Sommario

Viene rivisto alla luce dei dati della letteratura e della casistica personale il ruolo della timectomia nella terapia della miastenia. Dei pazienti non portatori di timoma i migliori risultati si ottengono in quelli di età fra i 10 e i 40 anni con una durata della malattia minore di tre anni. Non vi è prevalenza di sesso. Ci si può attendere un miglioramento duraturo. Non vi sono prove di una correlazione tra gli indici biologici germinativi quali i centri germinali nel timo e o il titolo degli anticorpi contro i ricettori acetilcolinici e il decorso post-operatorio della malattia. È fondamentale la completa asportazione del timo e perciò è preferibile la scelta della tecnica di approccio transternale.

Nei pazienti con timoma la timectomia è meno efficace ma l'intervento è necessario per evitare danni derivanti dall'infiltrazione del timoma sugli organi circostanti. Il perché della efficacia della timectomia nei pazienti con un timo attivo ma non in quelli con timoma potrà essere chiarito dagli studi in vitro sulle interazioni tra cellule timiche e quelle periferiche B, studi che sono ormai in stadio avanzato.

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