Surgical treatment of myasthenia gravis in two major Middle East teaching hospitals: factors influencing outcome

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Abstract

Background **–The results of thymectomy on patients with generalised myasthenia gravis have been widely reported. However, there is no information on whether the experience of western countries can be generalised to the population of the Middle East. The purpose of this study was to evaluate the safety and efficacy of thymectomy in patients with myasthenia gravis in a Middle East patient population and to identify clinical and histopathological factors associated with improved long term outcome of surgery.**

Methods **– In a prospective study, sixty three patients (aged 1·5–51 years) were treated in two university teaching hospitals between 1984 and 1991 and followed up for a mean of four years. Close communication was established with neurologists to obtain early referral. Radical anterior mediastinal dissection through a median sternotomy was performed in all patients. The response was evaluated by modified Osserman's classification.**

Results **– Eighteen patients achieved complete remission and a further 39 improved, producing an overall response rate of 90·5%. Patients with milder disease (stage II) had a higher response rate (97%) than those with more advanced disease (78%). Patients operated on with less than three years of symptoms had a better outcome (94%) than those with longer duration of preoperative symptoms, especially in non-thymomatous patients. Age and sex had no effect on the outcome. There was no effect on response rate if patients had hyperplastic or non-specific thymic histological findings, but patients with thymoma fared worse.**

Conclusions **– These results are comparable with reports from the western world and represent the first prospective study from the Middle East. Thymectomy is indicated for all patients suffering from generalised myasthenia gravis soon after the diagnosis is made, regardless of age, stage, thymic pathology, and preoperative clinical status.**

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Myasthenia gravis is an autonomic disorder directed against postsynaptic acetylcholine receptors which causes weakness and easy fatiguability of voluntary muscles. The excellent outcome following thymectomy reported in many series has established this procedure as the mainstay of treatment in patients with myasthenia gravis.[1–6] Thymectomy typically removes the major source of antibody production and offers the best chance of remission.[7] Improvement has been reported in 80–90% of patients after surgery.[8]

However, there is still no general agreement about which patients would benefit most from the removal of the thymus.[9,10] Our aim was to evaluate the influence of some of the factors known to be controversial for outcome after thymectomy in patients with myasthenia gravis in a Middle East patient population. We were also interested to know the safety and efficacy of this procedure and the clinical course of 63 consecutive patients with myasthenia gravis treated with thymectomy is reviewed.

One important issue is the timing of surgical intervention in these patients. Most neurologists advocate thymectomy for selected patients with generalised myasthenia gravis without thymoma.[11] To support the practice of early referral for surgical treatment of patients with myasthenia gravis we communicated closely with the department of neurology responsible for the care of these patients in the region.

Methods

The study was designed prospectively to assess the remission and response rate as well as the safety of thymectomy in patients treated in two university affiliated teaching hospitals. Sixty three patients with generalised myasthenia gravis were operated on between 1984 and 1991. The procedures were performed by the same surgical team in two tertiary medical centres, Shohada and Khatam centres in Iran.

Some of the controversial factors which may have an effect on the outcome in patients with myasthenia gravis undergoing thymectomy were evaluated including age, sex, duration of symptoms, thymic pathology, disease severity, and the amount of preoperative medication.

The diagnosis was established on the basis of history and physical findings, and a positive tensilon (edrophonium) test. In some patients adjuvant diagnostic tests were also used (Jolly test, electromyography (EMG), and acetylcholine receptor (AChR) antibody). All patients were evaluated for other possible associated conditions – for example, thyroid auto-

Table 1 Osserman classification of 63 patients with myasthenia gravis according to disease severity

Class	Symptoms	No. of patients (%)
I	Ocular involvement only	0 (0)
IIA	Generalised muscular involvement without respiratory impairment	8 (12·8)
IIB	More bulbar manifestations than group IIA	32 (50·8)
III	Rapid onset and progression of bulbar and generalised disease with respiratory muscular weakness	21 (33·3)
IV	Progressive symptoms developing at least two years after the patient has been in group I or II	2 (3·1)

Table 2 Grade of response according to modified Osserman scale in 63 patients

Response grade	Definition	No. of patients (%)
A	Complete remission for more than 90 days	18 (29)
B	Symptom-free on decreased dose of medication	28 (44)
C	Marked clinical improvement with no change in medications	11 (18)
D	No clinical improvement with same dose of medication	4 (6)
E	Clinically worse	2 (3)

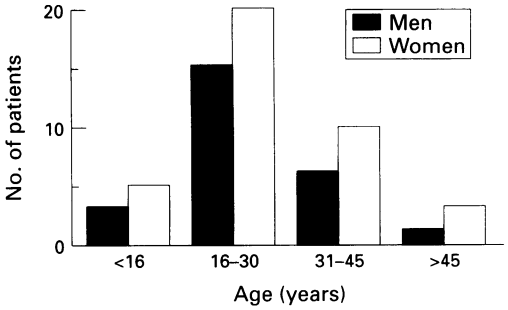
immune disorders, thymoma, collagen vascular diseases, red cell aplasia, and multiple sclerosis. One patient also had Grave's disease and two had migraine.

The patients were divided into three groups based on the duration of the preoperative symptoms: <1 year, 1–3 years, and >3 years. The Osserman classification[12] was used to group the patients according to the severity of their disease (table 1).

All the patients were followed up at intervals of three months for the first year and yearly thereafter for a range of 2–8 years. The response to surgery was recorded at the last check up and the patients were classified by a modified Osserman's[12] response to thymectomy (table 2). Asymptomatic patients receiving no medical treatment for more than three months (grade A) were considered to be in remission. Patients in remission (grade A), symptom-free patients on decreased doses of medication (grade B), and patients with significant clinical improvement with the same dosage of medications as before surgery (grade C) were all considered to have responded to thymectomy. The remission and response rates between the different groups were compared using the χ^2 test.

All the patients with an established diagnosis of generalised myasthenia gravis underwent surgery as soon as was convenient regardless of stage or admission status of their disease. Three were resected while they were intubated on mechanical ventilation due to respiratory insufficiency.

Plasmapheresis was performed perioperatively in 17 patients (all stage III or IV) after 1985, usually starting 2–4 days before surgery and extending into the postoperative period with up to five procedures (4–12 days). Normal saline and/or 5% albumin was used as the plasma replacement solution.



Age and sex distribution of 63 patients with myasthenia gravis

OPERATION

The operation was performed through a complete median sternotomy. Mediastinal dissection began from the lowest part of the anterior mediastinum but not beyond the phrenic nerves. If prominent lymph nodes were present around these nerves they were isolated and the lymph nodes and their adjacent fatty tissue included en bloc with the specimen. The dissection continued cephalad until the lower portion of the thyroid was reached.

The patients were weaned from the ventilator when continuous pulse oximetry, serial evaluation of arterial blood gas tensions, lung volume and mechanics, and ability to protect airway or control secretions permitted. The patients were extubated according to the same parameters and his/her response to the weaning process.

Tapering of medications did not have a standard protocol as different strategies were used by the various neurologists involved. In some patients treatment started 1–3 days after surgery and decreased as symptoms decreased, while in others, especially those with more mild disease, the dosage was started as low as possible and increased to an optimum over the hospital stay or next clinical visit and modified again at future visits.

Results

Thirty four of the patients (54%) were women and the age range was 1·5–51 years (mean 25·7). Eight patients were under 15 years of age, of whom four were aged 1·5–4 years. The mean age of the patients older than 15 years was 28·2 (figure). The interval between the onset of symptoms to surgery was 4–180 months (median 21). None required perioperative blood transfusion and the average amount of blood loss was less than 300 ml.

Seven patients with class IIA disease were taking no medication before surgery. Twenty nine patients were treated with neostigmine or pyridostigmine, eight were on steroids, and another 19 were treated by both medications preoperatively.

There was no operative mortality. Forty six patients were extubated in the recovery room, 14 of whom were not admitted to the ICU and were returned to the surgical ward. In seven patients intubation was continued for 1–7 days postoperatively (mean 3·7 days) including the

Table 3 Effect of different variables on prognosis after thymectomy in 63 patients

Variable	*No. of patients*	*No. of patients in remission*	*No. of patients responded*
Sex			
Men	25 (40)	6 (24)	24 (96)
Women	38 (60)	12 (33)	33 (87)
Age (years)			
1–15	8 (13)	4 (50)	8 (100)
16–30	35 (56)	8 (23)	31 (89)
31–45	16 (25)	4 (25)	14 (87)
>45	4 (6)	2 (50)	4 (100)
Duration of symptoms (years)			
<1	26 (41)	7 (27)	25 (96)
1–2	25 (40)	8 (32)	23 (92)
>3	12 (19)	3 (25)	9 (75)*
Preoperative stage			
IIA	8 (13)	3 (38)	8 (100)
IIB	32 (51)	12 (38)	31 (97)
III	21 (33)	3 (13)	17 (80)
IV	4 (3)	0 (0)	1 (25)†
Non-thymomatous pathology			
Hyperplasia	30 (48)	10 (33)	28 (93)
Non-specific	28 (44)	8 (28)	26 (93)
Thymoma	5 (8)	0 (0)	3 (60)‡

Numbers in parentheses are percentages.
* $p<0.05$ patients with <3 years *v* >3 years preoperative duration of symptoms
† $p<0.05$ stage II *v* stage III and IV.
‡ $p<0.05$ for thymoma *v* non-thymoma.

three patients who were already intubated preoperatively. Two patients developed cholinergic crises. The average length of hospital stay for all patients was 4–30 days (mean 8·1 days).

In three patients there was thymic tissue outside the main gland. Of these, it was in the fatty tissue between the lower thymic lobe and diaphragm in two and in one of these there was a 1 cm fibrous connection to the right lower pole of the thymus. In the third case the postoperative histological report showed thymic tissue near the lymphatic tissue around the phrenic nerves.

The surgical outcome based on the modified Osserman's classification is summarised in table 2. Complete remission (grade A) was achieved in 18 patients (28·5%) and a further 39 patients improved after surgery (grade B and C). Thus, a total response rate of 90·5% was achieved. Two women, both with class IIb disease, subsequently had three normal pregnancies; one was in complete remission and one had no symptoms on pyridostigmine 240 mg/day.

The effect of different variables on outcome is summarised in table 3. Patients operated on earlier in the course of their disease had a significantly better response (94%) than those who had had symptoms for more than three years (75%, $p<0.05$). In 58 patients who did not have a thymoma the response rate was even higher ($p=0.001$). Patients with milder disease had a better overall prognosis ($p<0.05$ for response rate). If the patients were operated on in stage II they had a much better likelihood of remission ($p<0.05$) and a better outcome ($p<0.05$) than those in stages III and IV.

Three groups of thymic disease were identified: five patients with thymoma (7·9%), 30 with hyperplasia (47·6%), and 28 with non-specific findings (44·4%). The latter group included children under four years of age and those with involuted thymus glands. There was no significant difference between patients with hyperplasia and non-specific pathological findings, although those with thymoma had a worse outcome ($p<0.05$).

Sex and age had no impact on remission or the improvement rate. There was no difference in outcome between the paediatric and older age groups.

Discussion

Since the first excision of a thymic cyst in a 19 year old girl with myasthenia gravis in 1939[13] thymectomy has gradually become accepted as the definitive treatment for generalised myasthenia gravis.[1 4–8] As the thymus gland is the source of antibodies against acetylcholine receptors, thymectomy is the only treatment that removes the cause of the disease. Patients with myasthenia gravis not treated surgically have a 40% mortality in 10 years with a median survival of seven years.[1] Based on a computer-matched study in 1975, Buckingham *et al* showed significantly superior results in patients undergoing thymectomy compared with those undergoing medical treatment alone.[1] Our patients had a complete remission of 28·5% and an overall response to surgery of 90·5%, which is comparable with most published results[7 8] which range from 80% to 94%. The patients in our study were generally operated on at a more advanced stage of disease than were patients in studies which have reported a higher response rate.[14 15]

Three of our patients had thymic tissue (4·7%) separate from the main thymus gland. From the anatomy of these extrathymic remnants we believe that they would have been overlooked if a less aggressive surgical approach had been used. Jaretzki *et al* reported that thymic tissue was found in the mediastinum outside the main thymus gland in all but one dissection in their 50 patients.[16] Some other studies have also shown that more limited resections may result in retained thymic tissue.[17]

The effect of early surgical intervention after the onset of symptoms on the response rate is controversial. In a survey by Lanska[11] only four of 56 experienced neurologists advocated thymectomy in less than one third of their patients; 28 advocated it for between one third and two thirds, and 17 advocated it for more than two thirds of their patients. Most of the neurologists in that report advocated thymectomy for selected patients with generalised myasthenia gravis without thymoma. Some reports have shown no relation between the preoperative duration of symptoms and the outcome.[18 19] Our results and those of others [2 4 7 15 20 21] show that patients operated on early in the course of their disease have a better outcome. More than 80% of our patients were referred less than three years after the onset of symptoms. Patients operated on later during the study had a significantly shorter duration of symptoms than those seen earlier in the study.

Hatton *et al*[22] and Barton *et al*[23] reported that patients with more advanced disease benefited more from thymectomy, while others [7 8 19] found that the stage of the disease had no effect on

outcome. Our results and those of others[4 18 21 24] suggest a more favourable outcome in patients with a milder form of myasthenia gravis. Patients with advanced disease received more medication when admitted for surgery so a less favourable prognosis in patients on more drugs was attributed to a more advanced stage of the disease and not to the amount of preoperative medication itself.

Compared with most others, who have reported thymoma in 9–28% of their patients with myasthenia gravis, only five (8%) of our patients had a thymoma. In addition, although some authors have shown a better outcome in patients with thymic hyperplasia,[22] in our series and others[7 8 15 19–21 23] there was no difference in remission or response between patients with germinal layer hyperplasia and those with a non-specific thymic histopathological report.

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