Outcome of thymectomy in patients with Myasthenia Gravis

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ABSTRACT

Objective: Myasthenia Gravis is a neuromuscular disorder characterized by weakness and fatigability of skeletal muscles. Thymectomy is now beneficial even for non-thymomatous patients. The aim of this paper is to evaluate the role of thymectomy as on the treatment options for myasthenia gravis.

Methods: Thirty patients underwent thymectomy in the period from April 1999 through to July 2000. They were collected from different teaching hospitals in Baghdad, Iraq. All these cases were studied conventionally including history, physical and neurological examination in addition to investigations with particular emphasis on connective tissue screen and thyroid function test.

Results: The age in this study ranged between 17-55 years. The preoperative duration ranged between 2-20 months and the postoperative follow up period ranged between 6 months-14 years. The most favorable results were obtained in patients without thymoma with short duration.

Conclusions: Early thymectomy carries the best results in Myasthenia Gravis and every effort should be made to shorten the preoperative duration for both thymomatous and nonthymomatous patients. Patients with symptoms can be better controlled with anticholinesterase drugs than patients using steroid and cytotoxic drugs. Thymectomy is beneficial for most patients with Myasthenia Gravis and especially in those with benign folicular hyperplasia.

Keywords: Myasthenia Gravis, thymus, thymectomy.

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Myasthenia Gravis (MG) is a neuromuscular disorder characterized by weakness and fatigability of skeletal muscles. The underlying defect is a decrease in the number of available acetylcholine receptors (AChRs) at neuromuscular junctions due to an antibody-mediated autoimmune attack. The thymus is abnormal in 75% of patients with MG in 65% the thymus is "hyperplastic", and 10% of patients have thymic tumor (thymoma). The cardinal features are weakness and fatigability of muscles. The course of MG is often variable. Exacerbation and remission may occur, particularly in the first few years after the onset of the disease. Ocular muscles are the most frequently involved. Involvement of the other cranial nerves can result in dysphagia, nasal regurgitation, and aspiration. Overtime, 85% of patients develop generalized skeletal muscle involvement.[1,2] The thymus gland is a flattened, bilobed structure, lying in the anterior mediastinum between the sternum and the pericardium. In the newborn it reaches the largest size. It continues to grow until puberty, but thereafter undergoes involution. It has a pink, lobulated appearance, and is an important source of T-lymphocytes.[3] Sixty five percent of patients with MG show a striking degree of hyperplasia of lymphoid follicles and active germinal centers confined to the medulla of the thymus. The cells in the centers of the follicles are histiocytes and they are surrounded by helper T-lymphocytes, B-lymphocytes and plasma cells, IgG is elaborated in germinal follicles.[3-6] Two forms of thymic tumors have been described, one is

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composed of reticular (histiocyte) cells like those in the center of the follicles, and the other is predominately lymphocytic and specified as lympho-sarcomatous.[2,5] The technical goal of thymectomy in the treatment of MG is complete removal of all the thymic tissue. Thymectomy is advisable in practically all patients with uncomplicated MG between puberty and 60 years of age, who after a period of treatment with anti-choline esterase drugs are responding poorly and require increasing doses of medication.[1,4,7] The remission rate after thymectomy in non-tumor patients is approximately 35% provided that the procedure is carried out in the first year or 2 after onset of the disease and an other 50% will improve to a certain extent. The remission rate is progressively lower if the operation is postponed beyond this time. The response for thymectomy is usually not evident for several months and is a maximal by 3 years.[2,5,8] Although onset and extent of improvement are unpredictable any weakness persistent one year after thymectomy is unlikely to remit without additional therapy. Contrary to the common perception the anatomy, the human thymus is complex. It consists of multiple lobes in the neck and mediastinum, often not contiguous, as well as gross and microscopic thymic tissue widely and invisibly distributed in cervical and mediastinal fat. Complete resection can not be ascertained by visual inspection at surgery, and gross and microscopic thymic tissue may be over-looked unless enblock resection is performed, both in the neck and in the mediastinum.[9,10] Total thymectomy is usually performed through a transternal approach.[10] The transcervical approach described by Lay Gooper may fail to achieve complete removal of all thymic tissue.[11-13]

Methods. Thirty patients underwent thymectomy (19 females and 11 males). These cases were studied conventionally including history, physical and neurological examination. All cases included in the study met the following criteria: 1. Post-operative evaluation was carried out after at least 6 months. Our criteria or grading for the estimation were based on those of Papatestas et al[14] i. Improved (without medication and asymptomatic). ii. With reduction of medication and clinically improved or both. iii. Stable disease with no clinical manifestation. iv. Presented a deterioration of their clinical status with deterioration of symptoms, required more medication or both. v. Died due to myasthenia. 2. All the cases included in this study were subjected to the following investigations, complete blood picture, serum electrolyte, liver function test, renal function test, chest X-ray, connective tissue screen including: deoxyribonucleic acid double stranded antibodies,

Table 1 - Age and gender distribution.

Sex	Age					
	10-20	**21-30**	**31-40**	**41-50**	**>50**	**Total**
Female	-	11	5	1	2	**19**
Male	1	7	2	1	-	**11**
Total	**1**	**18**	**7**	**2**	**2**	**30**
The mean age in this study is 29.5 years range between (17-55 years)						

Table 2 - Clinical presentation according to Osserman's classification preoperatively.

Pre-operative Grade	N of patients (%)
11 a	14 (47)
11 b	10 (33)
111	6 (20)
Total	**30 (100)**
N=number	

Table 3 - Features of nonthymomatous patients.

Features	Pre-operative grading Grade N	Post operative grading G1N G2N G3N
Ossermans classification	11 a 14 11 b 8 111 2	8 6 - 4 3 1 - 1 1
Age	20-51 years, mean 30 years	
Gender		N (%) Male 17 (71) Female 7 (29)
Duration	2 months to 20 months	
Macroscopic		N (%) Cyst 1 (4) Normal 23 (96)
Microscopic	Benign follicular hyperplasia	24
Follow up period	6 month - 14 years	
N=number, g=grade		

Table 4 - Relationship between the preoperative duration and the postoperative response grading according to the number of the patients for nonthymomatous patients.

Preoperative grading	Post operative grading for patients < 6 months			Post operative grading for patients > 6 months		
	G1 N	G2 N	G3 N	G1 N	G2 N	G3 N
11 a	5	6	-			
11 b	1	2	-	1	2	-
111	-	-	-	3	1	1
				-	1	1
Total	**6 (25%)**	**8 (33%)**		**4 (17%)**	**4 (17%)**	**2 (8%)**
G - group; N -number						

ANF, rheumatoid factor, and LE cells. Hormonal assays with a particular emphasis on thyroid function test (T3, T4, and TSH). The ancillary investigations include acetylcholine receptor antibodies, single fiber electromyograpgy, chest tomography and Computerized tomography (CT scan) or magnetic resonance imaging and CT scan of brain. 3. Symptoms and signs of any patients were studied retrospectively and prospectively depending on the case sheet, discharging card, and questionnaire of patients. 4. All the patients underwent thymectomy by transternal approach.

Results. **Table 1** presents the age and gender distribution of the patients. **Table 2** summarizes the preoperative clinical presentation according to Osserman's classification. **Table 3** outlines the features of nonthymomatous patients. The relationship between the preoperative duration and the postoperative response grading according to the number of the patients for nonthymomatous patient is shown in **Table 4**, and distribution of 6 patients with thymoma is shown in **Table 5**.

Discussion. The overall female:male ratio between F:M in this study was 1.57:1 and the peak incidence of Myasthenia gravis was between 21-30 years. The results are consistent with the previous studies.[15,16] All the nonthymomatous patients (24 patients) were classified according to Osserman's classification 14 in grade II a, 8 in grade II b, and 2 in grade III. In this study patients with grade 11a had a higher rate of remission more than grade 11b, and 111 as seen in Table 3, and this is consistent with the other studies.[4,17-19] Preoperative duration in this study was divided into 2 groups, less than 6 months and more than 6 months. The group with less than 6 months included 14 patients (58%) of nonthymomatous patients (10 females and 4 males). Six (43%) patients of them achieved grade 1, 8(57%) patients achieved grade 2. The 2nd group (more than 6 months) included 10 patients (42%) (7 females and 3 males), 4 (40%) patients achieved grade 1, 4 (40%) patient achieved grade 2, and the other 2 (20%) patients remained unchanged and achieved grade 3. The best remission rate and result occurred in patients with less than 6 months preoperative duration.

Table 5 - Distribution of 6 patients with Thymoma.

Age	Sex	Preoperative duration (months)	Macroscopic findings	Microscopic findings	Preoperative Ossermans classification	Postoperative grading criteria	Post operative follow up	CXR and CT scan finding	No. of crises or relapses	Causes of relapse
28	Male	3	Mass with capsule invasion	Malignant thymoma	11 b	4	6 months	No evidence of recurrence	-	-
27	Male	6	Encapsulated mass	Benign thymoma	11 b	3	1.5 years	No evidence of recurrence	-	-
23	Female	9	Encapsulated mass	Benign thymoma	111	4	5 years	No evidence of recurrence	2	URTI, TB-chest
55	Female	3	Mass with invasion of the capsule	Malignant thymoma	111	4	3 years	No evidence of recurrence	1	URTI pneumonia
28	Male	9	Mass with invason of the capsule	Malignant thymoma	111	5	4 years	-	3	Myelopathy TB chest, pericarditis, pleural effusion
17	Male	8	Mass with invasion of the capsule	Malignant thymoma	111	4	1.8 years	No evidence of recurrence	2	URTI pneumonia typhoid fever
CXR=chest x-ray, CT=computerized tomography, URTI=upper respiratory tract infection, TB=tuberculosis										

Drachman remarked that antibodies have been shown to reduce the number of available AChRs by accelerated endocytsis, degradation and function blockade of acetylcholine binding sites, which results in the fundamental defect and the flattening of the post-synaptic folds.[1] This is consistent with other studies, which concluded that the best prognosis was found in patients who had a high level of receptor binding sites and thymic hyperplasia and this is consistent with other studies.[17,20-22] All the nonthymomatous type had a normal looking preoperative gross appearance, apart from one patient, who had cystic changes, and on microscopical study, all the patients had benign hyperplasia. Myasthenia Gravis runs a fluctuating course with spontaneous relapses and remissions. Although remission occurs in 16% of patients and rarely exceeds 2.2 years.[4] Three patients remain stable postoperatively and need neither increase nor decrease of the preoperative medications, one with thymoma and the other 2 are nonthymomatous. Two nonthymomatous patients had severe symptoms prior to the operation, the first one treated for infection by aminoglycoside (garamycin), 2 weeks before the diagnosis of MG, while the 2nd one had an upper respiratory tract infection.[2] For the nonthymomatous type, postoperative follow up period ranged between 6 months – 14 years, during which period the patients remained in a remission state with no significant deterioration or required increasing of the drug dose. Six thymomatous patients were studied thoroughly. The diagnosis of thymoma was made preoperatively, and proved by microscopical examination. The preoperative duration ranged between 3-9 months. They included 2 benign and 4 malignant types. All of them were referred for deep x-ray therapy. Preoperative Osserman's classification includes 2 in grade II b, and 4 in grade III. The response postoperatively for the nonmalignant type were grade 3 and 4, while the other 4 patients of malignant type needed increasing of the doses of steroid and immunosuppressive drugs, and 3 of them became grade 4 postoperatively. In other studies, 65% of patients with nonmalignant thymomatous MG were free of myasthenic symptoms when evaluated 6 months to 7 years after maximal thymectomy.[2] Lovelace and Younger, 1997, in their studies postulated that maximal thymectomy with en-block exteneration of the tumor and all thymic tissue is the preferred procedure in patients with thymoma, with inspection of the entire chest cavity for tumor implants, also if reoperation is undertaken for persistent or recurrent symptoms, the maximal procedure should be performed regardless of the location of the original incision.[4] The presence of thymoma is associated a higher likelihood of more severe symptoms, and with less improvement after thymectomy,[2] and this is consistent with previous reports.[23,24] One patient died and became grade 5 postoperatively. The prognosis of patients with thymoma is dependent on clinical stage.[25] Two out of 3 patients with thymoma die within 5 years.[4] This is in agreement with previous reports.[24] One patient with nonmalignant type and 3 of malignant type had a frequent relapses mostly due to infection, an aggravating factor known to cause relapse in myasthenia.[23,26] We do not know whether this reflects the disease severity, or an associated immune suppressive therapy, which increases the incidence of infection. However, there was an up to 2 fold increased frequency of crisis observed in the patients with a thymoma.[2] No patients with thymoma had symptoms related to thymoma like chest pain, hemoptysis, cough, hoarseness of voice, or evidence of superior vena caval obstruction, and chest x-ray and CT or both of the chest revealed no evidence of recurrence. All patients with thymoma received a course of radiotherapy. In one series, 5-years relapsing rate after removal of thymoma was 53% in those patients not receiving radiation therapy, 0% in those receiving radiation therapy, especially for stage II and III thymoma.[7]

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