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Factors predicting surgical outcome of thymectomy in myasthenia gravis

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Abstract---Aim of the study is to evaluate predictors of outcome after thymectomy in the management of non thymomatous myasthenia gravis. One hundred patients who underwent thymectomy for myasthenia gravis in the period between June 2019 and September 2021 in Kasr Alainy hospitals were recruited to this study. Preoperative assessment included age, gender, co morbidities, MGFA classification, duration of symptoms from time of diagnosis till surgery, preoperative medication, preoperative plasmapheresis. All patients performed CT chest, electromyography, and acetyl choline receptor antibody titer before and after surgery. Thymectomy was performed either by transsternal or VATS approach with documentation of the extent of resection; primary outcome was assessment of improvement by MGFA classification and need for medication. Secondary outcome was postoperative complications. Complete stable remission was achieved in 5 patients, clinical and pharmacological improvements were achieved in 71 patients, 21 patients didn't improve and only 3 patients worsen after surgery. Finally, we found that early onset MG, absent preoperative comorbidity, performing extended thymectomy and reduction of

postoperative Acetyl choline receptor antibody titer were significant predictors of improvement of MG symptoms after thymectomy.

Keywords---myasthenia gravis, thymectomy, outcome, AChR Ab, MGFA.

Introduction

Thymectomy has a central role in the treatment of myasthenia gravis. It has been regularly performed in patients with myasthenia gravis since more than 80 years when Blalock and colleagues reported improvement of generalized MG in a 21-year-old woman after removal of a cystic thymic tumor.⁽¹⁾ Several studies have sought to identify patients who would have the greatest benefit from thymectomy postoperatively. Unfortunately, there are few conclusive studies clearly identifying which patient population most likely to benefit from surgical intervention.^(2,3,4,5) The study was designed to evaluate factors predicting surgical outcome of thymectomy in myasthenia gravis.

Patients and Methods

This was a prospective randomized observational study of one hundred patients who underwent thymectomy for myasthenia gravis in the period between June 2019 and September 2021 in Kasr Alainy hospitals to evaluate the predictors of success for thymectomy in nonthymomatous myasthenia gravis. All patients with myasthenia gravis who are indicated for thymectomy for non thymomatous myasthenia gravis were recruited in our study while the following patients were excluded from this study: the patients that was indicated for thymectomy for thymomatous myasthenia gravis, negative Acetyl choline receptor antibody and positive Anti MUSK antibody.

All patients in this study were evaluated preoperatively by careful history taking and complete examination to collect their data regarding: - age, gender, presence of any other comorbidities, symptoms and signs of myasthenia gravis including their onset and duration, classification according to myasthenia gravis foundation association classification (MGFA). Medications types and doses in addition to any previous need for plasmapheresis were reported. Moreover, Investigations were done as follow: routine labs, acetyl choline receptor antibodies level, electrophysiological studies and CT chest was done for all patients to exclude thymomatous myasthenia gravis.

All patients were done either via Video Assisted Thoracoscopic Surgery (VATS) utilizing the right side multiport approach or trans sternal thymectomy (TS thymectomy). All trans sternal thymectomy were with extended thymic resection including all pericardial fat from phrenic to phrenic laterally and from innominate vein superiorly to diaphragm inferiorly. however, some cases in VATS group were by simple thymic resection.

Patients were followed-up postoperatively in hospital and two times after surgery in outpatient clinic for 6 months. Data collection for postoperative mechanical

ventilation, ICU stay, total hospital stay, postoperative complications, general Outcome (complete remission, improvement, no improvement, worsening of symptoms), Need for medical treatment and Follow up Acetyl choline receptor antibodies level were documented.

Statistical Analysis

Statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA) was used to summarize data into: mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage). Non-parametric Kruskal-Wallis and Mann-Whitney tests were used to compare between quantitative variables⁶. Chi square (c2) test was performed to compare categorical data. Exact test was used instead when the expected frequency is less than 5⁽⁷⁾. *p*-values less than 0.05 were considered as statistically significant.

Results

Statistical analysis of 100 patients who underwent thymectomy revealed that there were 65 females (65 %) and 35 males (35 %). The mean age was 28.35 ± 10.67 years, divided into 2 age groups: 92 patients were less than 50 years old and 8 patients were more than 50 years old. There were only 3 patients (representing 3 %) had comorbidities; 2 patients were hypertensive and one patient was hypertensive and diabetic.

The mean duration of myasthenic symptoms from time of diagnosis until the time of surgery was 13.93 ± 10.5 months, divided into 2 groups: 63 patients had duration of symptoms less than 1 year and 37 patients had duration of symptoms more than 1 year. Preoperative MGFA classification of the myasthenic symptoms was shown in table 1 with Preoperative mean of AChR antibody was 2.39 ± 1.63 nmol/l

Table 1
Preoperative MGFA classification of the patients in the study

Pre operative MGFA Classification	Number	Percentage
I	3	3 %
IIa	26	26 %
IIb	37	37 %
IIIa	22	22 %
IIIb	10	10 %
Iva	1	1 %
Ivb	1	1 %

Preoperative medical treatment was classified as pyridostigmine only, pyridostigmine plus prednisolone and pyridostigmine plus azathioprine shown in table 2. 59 patients performed preoperative plasmapheresis while 41 patients did not perform plasmapheresis.

Table 2
Preoperative medication

Medications	Number	Percentage
Pyridostigmine	30	30.0%
Pyridostigmine and prednisolone	64	64.0%
Pyridostigmine and azathioprine	6	6.0%

Surgical approach was trans-sternal thymectomy in 30 cases and thoracoscopic thymectomy in 70 cases. Extended thymectomy was performed in 63 patients and simple thymectomy in 37 cases shown in table 3.

Table 3
Different Surgical approaches and techniques

Surgical approach and technique	Number	Percentage
VATS thymectomy	70	70.0%
Transsternal thymectomy	30	30.0%
Extended thymectomy	63	63%
simple thymectomy	37	37%

All patients were routinely admitted to icu with the mean Postoperative ICU stay 23.98 ± 7.79 hours. Only 7 patients transferred to ICU on mechanical ventilation while the remaining 93 patients transferred to ICU extubated with the mean mechanical ventilation (only 7 patients) time 34.85 ± 6.71 hours. The mean total hospital stay was 5.68 ± 2.33 days

Postoperative complications were 9 % including 1 case (1%) progressed to mortality (male patient 55 years old, diabetic and hypertensive, postoperative failure of weaning from mechanical ventilation and died from ventilator associated pneumonia). Four patients had superficial wound infection. One patient had chest wall sinus. , 3 patients had postoperative myasthenic crisis.

Postoperative symptoms by MGFA classification shown in table 4 also Postoperative medical treatment was shown in table 5 And The mean Postoperative AChR antibody was 1 ± 1.22 nmol/L.

Table 4
Postoperative MGFA classification

Post operative MGFA Classification	Number	Percentage
No symptoms	5	5 %
I	20	20 %
IIa	52	52 %
IIb	12	12 %
IIIa	5	5 %
IIIb	3	3 %

Iva	2	2 %
Ivb	1	1 %

Table 5
Postoperative medication

Medications	Number	Percentage
No medication	5	5 %
Reduction of preoperative dose of Pyridostigmine	24	24 %
Continue on the same dose of preoperative Pyridostigmine	1	1 %
Same dose of preoperative Pyridostigmine and reduction or stoppage of prednisolone	53	53 %
Continue on the same dose of preoperative Pyridostigmine and prednisolone	11	11%
Same dose of preoperative Pyridostigmine and reduction or stoppage of azathioprine	4	4 %
Pyridostigmine and prednisolone and azathioprine	2	2 %

Postoperative outcome was: 5 patients had complete remission of symptoms, symptoms improved in 71 patients, 21 patients had the same symptoms and 3 patients worsen after surgery.

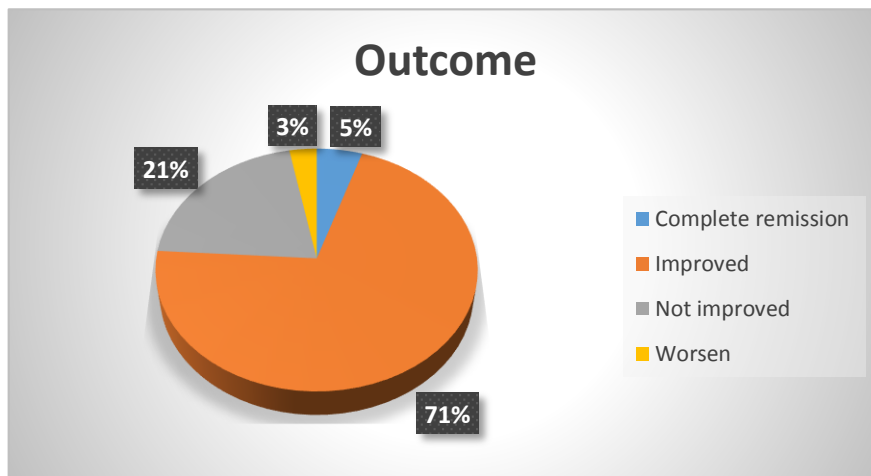


Figure 1. Outcome after thymectomy

Univariate analysis of the predictors of outcome after thymectomy revealed significant relationship between the outcome after thymectomy and

1. Age : early onset myasthenia gravis (less than 50 years old) has better outcome than late onset myasthenia gravis (more than 50 years old)
2. Preoperative comorbidity: presence of preoperative comorbidities increases risk after surgery.
3. Postoperative level of AChR antibody: reduction of postoperative level of AChR antibody is significant indicator for improvement and vice versa.

4. Extended resection of the thymus gland significantly improve outcome. Also, we found no significant relationship between outcome after thymectomy and gender, duration of symptoms, preoperative MGFA classification, preoperative medical treatment, preoperative plasmapheresis, preoperative level of AChR antibody level and different surgical approach.

Table 6
Factors affecting the outcome after thymectomy

		Outcome						P value
		Improvement		No improvement		Worsen		
		Number	Percentage	Number	Percentage	Number	Percentage	
Age group	<50	73	79.3%	17	18.5%	2	2.2%	0.025
	>50	3	37.5%	4	50.0%	1	12.5%	
Sex	M	25	71.4%	8	22.9%	2	5.7%	0.486
	F	51	78.5%	13	20.0%	1	1.5%	
Co morbidity	HTN, DM	1	100.0%	0	0.0%	0	0.0%	0.044
	HTN	0	0.0%	1	50.0%	1	50.0%	
	No	75	77.3%	20	20.6%	2	2.1%	
Symptoms duration	<1 year	52	82.5%	10	15.9%	1	1.6%	0.117
	>1 year	24	64.9%	11	29.7%	2	5.4%	
Preoperative MGFA Classification	I	2	66.7%	1	33.3%	0	0.0%	0.072
	II	50	79.4%	13	20.6%	0	0.0%	
	III	23	71.9%	7	21.9%	2	6.3%	
	Iv	1	50.0%	0	0.0%	1	50.0%	
Medications	Pyridostigmine	23	76.7%	7	23.3%	0	0.0%	0.683
	Pyridostigmine and azathioprine	4	66.7%	2	33.3%	0	0.0%	
	Pyridostigmine and prednisolone	49	76.6%	12	18.8%	3	4.7%	
Surgical approach	VATS	30	90.9%	3	9.1%	0	0%	0.289
	transsternal	24	80%	6	20%	0	0%	
Simple versus extended thymectomy	simple	21	56.8%	13	35.1%	3	8.1%	0.001
	extended	55	87.3%	8	12.7%	0	0.0%	
Pre plasmapheresis	no	47	79.7%	12	20.3%	0	0.0%	0.113
	yes	29	70.7%	9	22.0%	3	7.3%	

Table 7
Relationship between AchR Ab Titre and outcome

		Outcome			P value
		Improvement	No improvement	Worsen	
Preoperative AchR Ab	Mean	2.43	1.98	2.57	0.287
	Standard Deviation	1.57	1.52	0.46	
	Median	2.30	1.40	2.30	
	Minimum	0.70	0.60	2.30	
	Maximum	6.30	5.70	3.10	
Postoperative AchR Ab	Mean	0.83	0.93	1.86	<0.001
	Standard Deviation	0.93	0.33	1.04	
	Median	0.45	0.9	1.82	
	Minimum	0.10	0.5	0.84	
	Maximum	4.00	1.6	2.92	

Discussion

After reviewing of one hundred cases underwent thymectomy for the management of non thymomatous myasthenia gravis with different surgical approaches we found that 5 patients representing 5 % had complete stable remission (CSR defined when patients were asymptomatic on no medication), 71 patients improved (improvement defined by having no or less symptoms on less or the same preoperative medication), 21 patients not improved, 3 patients worsen after thymectomy.

Although high incidence of myasthenia gravis in females and improvement in females was more than males but improvement rates among different gender is still not significant. Also El-Medany et al in 2003⁸ and Geng et al in 2020⁹ didn't find gender as an independent factor for outcome after thymectomy.

However, age was a significant predictor factor for outcome after thymectomy. As the improvement rate was 79.3% in young patients (less than 50 years old) and 37.5 % in the older patients (more than 50 years old). That was consistent with El-Medany et al in 2003⁸ and Yang et al in 2017¹⁰. Even in Japanese guidelines for management of myasthenia gravis they consider Thymectomy is not first line treatment for LOMG, and should be considered carefully in these cases as reported by Murai in 2015¹¹.

In our study, we found that preoperative comorbidities were a significant predictor of outcome after thymectomy as from 3 patients had comorbidities (hypertension, diabetes) one died and another one not improved that goes in side with Misra et al in 2020¹² who reported that Management of myasthenia gravis (MG) in the presence of comorbidities may be difficult.

Data from our study revealed that there were 63 patients with less than 1 year myasthenic symptoms before thymectomy and 37 patients with more than 1 year myasthenic symptoms before surgery with improvement rate 82.5 % and 64.9 % respectively. Although there were no significant statistical difference, but still early referral for surgery has a better outcome which is consistent with Nieto et al in 1999¹³ and contrary to El-Medany et al in 2003⁸

Based on MAGFA classification, our patients were distributed into 3 patients in class I , 63 patients in class II, 32 patients into class III and 2 patients in class V with improvement rates 66.7 % , 79.4 % , 71.9 % and 50 % respectively therefore the relation between the severity of symptoms and surgical outcome was suggestive but not significant. (p value 0.07). So we agreed with leuzzi and colleagues in 2014¹⁴ when they reported that their study showed a strong correlation between POMCs and Osserman-stage equal to or higher than III. As our patients in class V had 50% improvement and 50% worsen.

In our study, correlation between Acetylcholine receptor Antibody and outcome revealed that preoperative level didn't significantly affect the outcome in contrary to postoperative titer which was highly significant predictor. Many researches investigated AChR Ab as a predictor for severity of the disease and as a prognostic factor for improvement after surgery. They all concluded that preoperative titer level does not correlate with the severity of the symptoms nor to postoperative outcome. However, reduction of postoperative antibody Titre is a sensitive predictor factor for complete resection of the thymus thus reflecting better outcome after surgery as reported by kim et al in 2018¹⁵

In our study, 59 patients performed preoperative plasmapheresis, and 41 patients did not perform with improvement rate 70.9% and 79.7% respectively. Therefore, no significant relationship between preoperative plasmapheresis and postoperative outcome. Also Saeteng et al in 2013¹⁶ who reported that elective thymectomy without preoperative plasmapheresis in myasthenia gravis patient regardless of a history of myasthenic crisis did not affect the overall outcome.

In our study, comparison between different surgical approaches either by trans sternal or VATS thymectomy, and after exclusion of simple VATS thymectomy group to avoid bias, Showed no statistical significant difference in the outcome as improvement rate was 80% in trans sternal group and 90% in VATS also Bagheri et al in 2019¹⁷ reported that VATS thymectomy is a safe and appropriate approach comparing with traditional TS thymectomy with better results after surgery.

However, In Comparison between extended versus simple thymectomy. We found a statistical significant difference in the outcome as Improvement rate in extended group (87.3%) was much better than simple group (56.8%). Therefore, we agree

with LI et al in 2019¹⁸ who reported that extended thymectomy has been considered the goal of surgery for myasthenia gravis.

Conclusion

Our data analysis of multiple factors showed significant better outcome after thymectomy in early onset myasthenia gravis (less than 50 years old), after extended thymectomy and cases that showed AChR antibody reduction after surgery. Additionally, patients with comorbidities showed significant bad outcome. Also we found suggestive but not significant relationship between outcome and preoperative MGFA classification since severe cases showed bad outcome. In this study, we found no significant relationship between outcome after thymectomy and gender, duration of symptoms, preoperative plasmapheresis, preoperative level of AChR antibody and different surgical approach.

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