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Myasthenia Gravis: Clinical Aspects and Prognosis Following Thymectomy - in Aspect of Bangladesh

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Research Article

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Abstract

Background: Medical treatment for myasthenia gravis (MG) involves the use of anticholinesterase agents, immunosuppressive drugs, plasmapheresis, and gamma globulin. However, these agents result in a complete clinical remission rate as low. As a consequence, thymectomy, preferably by transsternal approach, has become increasingly accepted as an efficacious procedure for MG, with reported complete clinical remission rates as high.

Objective: To assess the clinical aspects of myasthenia gravis and prognosis following Thymectomy.

Methods: This prospective study was carried out on patients diagnosed as Myasthenia Gravis was evaluated by detailed history and examination who admitted in the above Department during the period from May 2013 to April 2015. Total number of patients was 16 and they were divided into two groups: Group A and Group B. Group A considered patients without plasmapheresis or immunoglobulin therapy (n=10) and Group B considered patients with plasmapheresis and/or immunoglobulin therapy (n=6). Statistical analyses were carried out by using the Statistical Package for Social Sciences version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Unpaired t-test, fisher's exact test, Chi-Square test with used to analyse the categorical variables, shown with cross tabulation. P values <0.05 considered as statistically significant.

Results: The mean age of the respondents was 34.9 years and 27.3 years by group A and group B respectively. Regarding the duration of disease in group A 50% of the patients had duration of disease >1 year and 66.7% in group B. Diurnal variation was found 9(90.0%) in group A and 6(100.0%) in group B. In group A majority 9(90.0%) patients had ptosis and in group B, 6(100.0%) had proximal weakness of limb muscle. Regarding osserman grade, majority 7(70.0%) were grade II a in group A and 6(100.0%) were grade II b in group B. Moderate improvement was observed in 7(77.8%) patients in group A and 4(80.0%) in group B.

Conclusion: Extended thymectomy might be an effective and safe procedure for the treatment of myasthenia gravis. As per study findings, moderate improvement was observed in most of the patients treated with thymectomy.

Keywords: Myasthenia Gravis; Acetylcholine; Electromyography; Intravenous Immune Globulin

Abbreviations: MG: Myasthenia Gravis; Ach: Acetylcholine; EMG: Electromyography.

Introduction

Myasthenia gravis is a relatively rare autoimmune disorder in which antibodies form against acetylcholine (ACh) nicotinic postsynaptic receptors. The basic pathology is reaction between acetylcholine receptors (AchRs) with anti-AchR antibodies. Thus blockage and reduction in the number of acetylcholine receptors occurs due to specific reaction. The blockage and reduction of AchRs results, characteristic pattern of progressively reduction of muscle strength [1]. The estimated prevalence of myasthenia gravis is approximately 20 cases per 100,000 populations in USA. The common age at onset is the second and third decades in women and the seventh and eighth decades in men and women are more often affected than men [2].

The presentation and progression of myasthenia gravis (MG) vary. About 80% of patients will subsequently develop more generalized weakness [3]. Extraocular muscle weakness or ptosis is present initially in 50% of patients and occurs during the course of illness in 90% [1]. Bulbar weakness can manifest as difficulty in chewing, slurred or nasal speech, dysphagia or nasal regurgitation of liquids. Weakness is more remarkable in the upper limbs than the lower limbs. The severity of the weakness typically fluctuates during day being least severe in the morning and worse as the day progresses [3].

The most serious complication is myasthenic crisis that is acute respiratory failure resulting from myasthenia gravis requires mechanical ventilation. This serious complication occurs in about 20% of patients with myasthenia gravis [3,4]. Thymic abnormalities are clearly associated with myasthenia gravis but the nature of the association is uncertain. Ten percent of patients with myasthenia gravis have a thymic tumor and 70% have hyperplastic changes (germinal centers) that indicate an active immune response [2,5,6]. Thymectomy is recommended for the treatment of the myasthenia gravis. The favorable response generally occurs 2 to 5 years after surgery. However the best response observed in young patients; early in the course of their disease. Patients without thymoma respond well than patients with thymoma following thymectomy [2]. Among myasthenia gravis patients who suffer with severe symptoms and sorter durations of disease, they showed greater degree of improvement after thymectomy [7].

In Bangladesh, rarity of the disease invited a very few research works in this field. This research revealed the pattern of presentation of MG among our population, which provided us the information regarding this disease. The knowledge of this particular disease profile also enables physicians to increase accuracy of diagnosis of this rare disease. Evaluation of the patients before and after thymectomy, provided degree of improvement of the patient that was achieved through this treatment. Factors that affect the postsurgical outcome was also be analyzed. Therefore this study revealed the pattern of presentation, investigatory findings, treatment history, early management for thymectomy and their improvements as well as factors related to outcome following thymectomy in MG patients.

Materials and Methods

Bangabandhu Sheikh Mujib Medical University is the only medical university in Bangladesh and the department of Cardiac Surgery of Bangabandhu Sheikh Mujib Medical University started its Journey in 2004. Since then it has become the leading cardiac surgery center of Bangladesh. This prospective study was carried out on patients diagnosed as Myasthenia Gravis was evaluated by detailed history and examination who admitted in the above Department during the period from May 2013 to April 2015. Total number of patients was 16 and they were divided into two groups: Group A and Group B. Group A considered patients without plasmapheresis or immunoglobulin therapy (n=10) and Group B considered patients with plasmapheresis and/or immunoglobulin therapy (n=6). The proposed study protocol was approved by the ethical committee of Bangabandhu Sheikh Mujib Medical University. Exclusion

criteria include: Eaton-Lambert syndrome, Bronchial asthma, pseudocholinesterase deficiency, Congenital myasthenic syndrome, progressive restricted myopathies, steroid and inflammatory myopathies, motor neuron disease, Multiple sclerosis, variants of Guillain-Barre syndrome (e.g., Miller-Fisher syndrome), Organophosphate toxicity, Stroke and Medications: neuromuscular blocking agents, aminoglycosides, penicillamine, antimalarial drugs, colistin, streptomycin, polymyxin B, tetracycline. EMG and antibody to acetylcholine receptor were assessed. Later preoperative evaluation was done and Thymectomy was performed. Extended thymectomy was performed in most of the cases. Standard median sternotomy was done. Thymus was identified. Phrenic nerves and innominate vein identified and preserved. Blunt dissection of overlying mediastinal pleura done. Thymectomy was done along with removal of periglandular, epipericardial, peripleural and supradiaphragmatic pad of fat. Excised thymus was sending for histological study just after the operation, using formalin preservative. In this study intravenous immunoglobulin was given postoperatively in only one patient. Following thymectomy the parameters of severity that is osserman's classification were assessed every monthly interval for 6 months and changes were recorded.

Statistical analyses were carried out by using the Statistical Package for Social Sciences version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Categorical variables were presented in the form of frequency and percentage and quantitative data was presented in the form of mean and standard deviation. The results were presented in tables, figures. Unpaired t-test, fisher's exact test, Chi-Square test with used to analyze the categorical variables, shown with cross tabulation. P values are <0.05 considered as statistically significant.

Results

In group A, less than half (40.0%) of the patients were in 4th decade and in group B more than three quarter (83.3%) of the patient belonged to age group 3rd years. Sex incidence was 68.75% male and 31.25% female Table 1.

Clinical presentation	Group A (n=10)		Group B (n=6)		p Value
	n	%	n	%	
Symptoms					
Dropping of eyelid	9	90.0	5	83.3	0.625^{ns}
Double Vision	6	60.0	3	50.0	0.548^{ns}
Weakness in chewing	5	50.0	5	83.3	0.215^{ns}
Difficulty in swallowing	5	50.0	2	33.3	0.451^{ns}
Slurring of speech	2	20.0	2	33.3	0.489^{ns}
Weakness in upper limbs	8	80.0	5	83.3	0.696^{ns}
Weakness in lower limbs	3	30.0	1	16.7	0.510^{ns}
Generalized weakness and fatigue	6	60.0	5	83.3	0.346^{ns}
Diurnal variation	9	90.0	6	100.0	0.625^{ns}
Sign					
Ptosis	9	90.0	5	83.3	0.625^{ns}
Weakness of facial muscle	5	50.0	2	33.3	0.451^{ns}
Voice change	1	10.0	2	33.3	0.303^{ns}
Proximal weakness of limb muscle	8	80.0	6	100.0	0.357^{ns}

ns= not significant
p value reached from fisher's exact test.
n= number of patients
Table 1: Distribution of the patients according to clinical presentation (symptoms and sings) in group A (n=10) and in group B (n=6), Total n=16.

Positive Ach R antibody was found 7(70.0%) in group A and all patients (100.0%) in group B. Positive electrophysiological study was 3(30.0%) in group A and 5(83.3%) in group B. Normal chest X-ray (CXR) was found 7(70.0%) and 5(83.3%) in group A and group B

respectively. In chest CT scan mediastinal mass was found 6(60.0%) in group A and 5(83.3%) in group B.

More than three quarter patients (90.0%) in group A and all patients (100.0%) in group B were taking Pyridostigmine Bromide and Neostigmine Bromide respectively. While four patients (40.0%) in group A and three patients (66.7%) in group B were taking corticosteroids. The difference was not statistically significant (p>0.05) between two groups Table 2.

Histopathological findings	Group A (n=10)		Group B (n=6)		p value
	n	%	n	%	
Normal	3	30.0	0	0.0	0.318ns
Atrophic	0	0.0	0	0.0	
Hyperplasia	3	30.0	3	50.0	
Thymoma	4	40.0	3	50.0	

Table 2: Distribution of the patients according to histopathological findings in group A (n=10) and in group B (n=6), Total n=16.

Postoperative complications occurs Myasthenic crisis in one patient (16.7%) in group B, Cholinergic crisis in one patient and hoarseness of voice in one patient. Hoarseness of voice and cholinergic crisis were categorized as others post operative morbidity (20.0%) in group A. There was no per-operative mortality. Two patients died in early post-operative period, one (10.0%) in group A and one (16.7%) in group B. The difference was not statistically significant (p>0.05) between two groups Table 3&4, Figure 1-3.

Osserman grade	Group A (n=9)		Group B (n=5)		p value
	n	%	n	%	
1st month					
Grade I	6	66.7	2	40.0	0.326ns
Grade II a	2	22.2	3	60.0	
Grade II b	1	11.1	0	0.0	
2nd month					
Grade I	6	66.7	3	60.0	0.627ns
Grade II a	2	22.2	2	40.0	
Grade II b	1	11.1	0	0.0	
3rd month					
Grade I	7	77.8	3	60.0	0.480ns
Grade II a	2	22.2	2	40.0	
4th month					
Grade I	6	66.7	2	40.0	0.295ns
Grade II a	2	22.2	2	40.0	
Grade II b	0	0.0	1	20.0	
5th month					
Grade I	7	77.8	2	40.0	0.238ns
Grade II a	2	22.2	2	40.0	
Grade II b	0	0.0	1	20.0	
6th month					
Grade I	7	77.8	2	40.0	0.238ns
Grade II a	2	22.2	2	40.0	
Grade II b	0	0.0	1	20.0	

ns = not significant, P value reached from chi square test
n=number of patients
Table 3: Distribution of the patients according to Osserman grade post operatively in group A (n=9) and in group B (n=5), Total n=14.

Outcome	Group A (n=9)		Group B (n=5)		p value
	n	%	n	%	
Clinically changed					
Yes	9	100.0	4	80.0	0.357ns
No	0	0.0	1	20.0	
Moderate improvement					
Yes	7	77.8	4	80.0	0.725ns
No	2	22.2	1	20.0	
Significant improvement					
Yes	1	11.1	1	20.0	0.604ns
No	8	88.9	4	80.0	

ns=not significant
p value reached from fisher's exact test
n=number of patients
Table 4: Distribution of the study patients according to outcome in group A (n=9) and in group B (n=5), Total n=14.

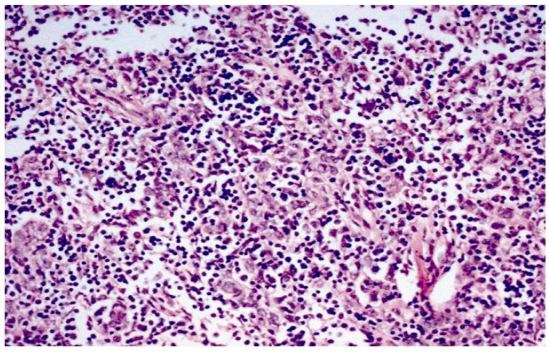

Figure 1: Figure shows thymic hyperplasia.

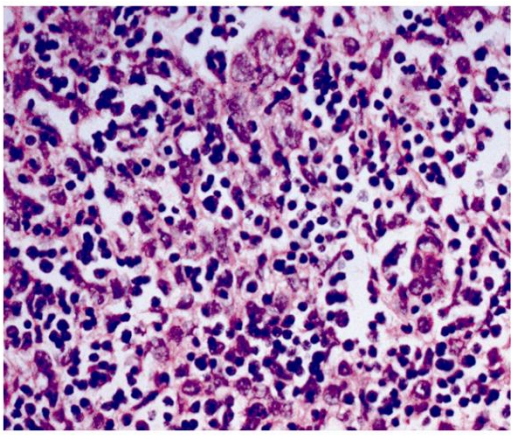

Figure 2: Figure shows type B1 thymoma.

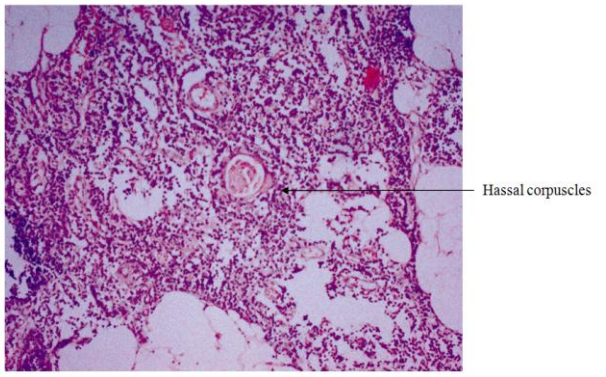

Figure 3: Figure shows normal thymic tissue.

Discussion

Myasthenia gravis affect individuals at any age group; women are more often affected than men. Howard [2] mentioned that the common age at onset is the second and third decades in women and the seventh and eighth decades in men. Grob, et al. [8] found that highest numbers of patients were over 20 years of age and their mean age was 44 years, which is higher with the current study, may be due to geographical and racial influences may have significant influence on Myasthenia Gravis.

Takanami, et al. [7] highlighted the duration of disease ≤24 months in 77.8% and >24 months 22.2%, which are comparable with this study. The present study clinical presentation of symptoms and sign are corresponds with Grob and his colleagues [8]. In this study out of 16 patients, two patients suffering from hyperthyroidism and one patient had hypertension and DM respectively.

Application of Osserman classification yielded: grade I, 3.3% patients; grade II a, 31.1%; grade II b, 62.3%; and grade III, 3.3% observed by Nieto, et al [9], which is comparable with the current study.

Kagotani, et al. [10] highlighted the importance of AchR antibodies both as a prognostic factor and as a determinant feature the course of future therapy after thymectomy. This study did not found any significant deference in the outcome based on presence or absence of AchR antibodies. Positive Electromyography (EMG) results of the current study mostly consistent with Howard [11]. Two patients were found with mediastinal mass (20.0%) and one with hilar lymphadenopathy (10.0%) in group A evaluated by X-ray chest posterior-anterior view. Rest of the patient revealed no abnormality in this study. While Chest CT scan revealed mediastinal mass in six patients (60.0%) in group A and five patients (83.3%) in group B. A study conducted by Vachlas, et al. [12], they highlighted that the proportion of thymoma patients who suffer from MG varies between 20% and 65%. Almost one third of cases are found incidentally on radiographic examinations during preoperative workup. This is comparable with this study.

A study conducted by Nieto, et al. [9], they reported anticholinesterase agents, such as pyridostigmine bromide, which have proved efficacious for neuromuscular transmission improvement; corticosteroids, immunosuppressives, and plasmapheresis for serum antibody concentration reduction, ultimately improve weakness episode. Their results were consistent with this study.

El-Medany et al. [13] reported that thymectomy has shown a strong correlation with outcome. They also highlighted, thymic histology is also consistent predictor of response. Hyperplasia correlates increase in improvement rate. Their results were mostly consistent with this study. Post operatively patient evaluated at one month interval for 6 months. In this study clinically unchanged was found in one patients (20.0%) in group B; Moderate improvement was found in seven patients (77.8%) in group A and four patients (80.0%) in group B; Significant improvement observed in one patient (11.1%) in group A and one patient (20.0%) in group B. The difference was not statistically significant ($p>0.05$) between two groups. These findings are mostly consistent with the findings of other studies conducted by Gajdos, et al. [14] and Yeh and Chiu [15]. Postoperative complications occurred and perioperative mortality in this study was consistent with studies conducted by Bedlack [4].

The present study population was selected from one selected hospital in Dhaka city with a very short period of time as well as small sample size was also a limitation of the present study. Plasmapharesis and immunoglobulin cannot be given in all patients in group B due to expense of the procedure. Further studies can be undertaken with bigger sample size in different institutional facilities.

Conclusion

As per study findings, moderate improvement was observed in most of the patients treated with thymectomy. Although some of post operative complications and two fatal consequences experienced by the patients. However, the issue needs to be justified by further clinical trial with larger sample of population with long duration.

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