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Prognostic Factors of Myasthenia Gravis Remission After Thymectomy at National Referral Hospital in Indonesia

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Abstract

Introduction. Thymectomy is a recommended treatment for myasthenia gravis, enfacing the problem of a low remission rate. However, Indonesian-specific characteristics of myasthenia gravis are somehow different from those of well-developed countries. Thus, identifying prognostic factors influencing remission is required for patient selection to provide optimal preoperative issues.

Methods. A retrospective cohort proceeded in our tertiary hospital, enrolling those diagnosed with myasthenia gravis who underwent thymectomy for four years. Disease period modified Osserman classification, age, sex, preoperative plasmapheresis, preoperative steroid therapy, type of surgery, and thymic pathology were the variables of interest for three-year follow-up. In addition, these variables were subjected to statistical analysis for prognostic factors.

Results. Twenty-six subjects completed the follow-up period with remission of 30.7% and associated with a period of suffering myasthenia gravis (p = 0.014) and the modified Osserman classification (p = 0.008). The disease period showed a specificity of 88.9% with a negative predictive value of 84.2% and a sensitivity of 62.5% with a positive predictive value of 71.4%. The modified Osserman classification showed a specificity of 83.2% with a negative predictive value of 88.2% and a sensitivity of 75% with a positive predictive value of 66.7%).

Conclusions. In our tertiary hospital, the disease period and the modified Osserman classification are prognostic factors of remission following thymectomy for myasthenia gravis.

Keywords: thymectomy, remission rate, modified Osserman classification

Introduction

Thymectomy is a recommended treatment in myasthenia gravis and showed a five-year postoperative clinical remission rate of 45%, which remains low (<50%).[1] thus, identifying factors influencing the remission after thymectomy is essential for patient selection to provide optimal preoperative care.

A study by Amin in Indonesia reported that thymoma is one of the causes of mortality in those with mediastinal mass (11.1%).[2] Previous studies showed eight identified prognostic factors for remission after thymectomy: age, gender, disease period, modified Osserman classification, preoperative plasmapheresis, preoperative steroid therapy, type of surgery, and thymic pathology. However, one should note that Indonesia has different characteristics than other studies in well-developed countries. Unfortunately, to date, no data on remission of myasthenia gravis following thymectomy and its prognostic factor in Indonesia. Thus, the study aimed to identify prognostic factors remission after thymectomy for myasthenia gravis in our tertiary hospital, dr. Cipto Mangunkusumo General Hospital (CMGH).

Method

The study proceeded retrospectively, enrolling patients who met the criteria who underwent thymectomy for myasthenia gravis from January 2014 to December 2018 who met the criteria. Those included were patients with myasthenia gravis who experienced thymectomy and had a three-year postoperative follow-up period. In contrast, those with pregnancy and those with carcinoma were excluded. Data were collected from medical records and reached out by telephone to find out the information, including 1) ocular symptoms (double vision or weak eyelids), bulbar symptoms (speech disability or swallowing disability), leg muscle weakness, and shortness of breath, 2) myasthenia gravis medication. These data were analyzed for sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio. The committee of ethics, Faculty of Medicine, Universitas Indonesia, approved the study (KET-890/UN2.F1/ETIK/PPM.00.02/2021) and protocol number 21-07-0787).

Results

Thirty–two patients diagnosed with myasthenia gravis underwent a thymectomy recorded. Out of this, 26 subjects with complete data were included; the other six were excluded due to incomplete follow-up. Subjects' characteristics are shown in Table 1.

Table 1. Subject characteristics

Variable	Frequency	Percentage (%)
Age	38 ± 15,6 years	N/A
≤40 years	14	53,8
≥40 years	12	46,2
Sex		
Female	18	69,2
Male	8	30,8
Disease duration	21 (1-96) months	N/A
≤12 months	7	26,9
>12 months	19	73,1
Modified Osserman classification		
Ocular weakness (I)	0	0
Mild general muscle weakness (II)	9	34,6
Moderate general muscle weakness (III)	15	57,7
Severe general muscle weakness (IV)	2	7,7
Respiratory insufficiency (V)	0	0
Preoperative plasmapheresis		
Yes	20	76,9
No	6	23,1
Preoperative steroid therapy		
Yes	26	100
No	0	0
Type of surgery		
Sternotomy (transsternal)	26	0
Transcervical	0	0
VATS	0	0
Thymus histopathology		
Thymic hyperplasia	7	26,9
Other	19	73,1

The median age was 39.5 years (3–64 years), dominated by females with disease periods varied from one to 96 months. Most of them had modified Osserman classification category of class II (34.6%) and III (57.7%), and no one with classes I and V. Most subjects received preoperative plasmapheresis (100%). In addition, all subjects received preoperative steroid therapy and underwent a sternotomy extended thymectomy procedure (transsternal). Histopathological findings showed thymoma in 14 subjects: 12 of class I and two of class II, and a small number with thymic hyperplasia. Eight subjects (30.7%) had remission, and the remaining 18 (69.3%) did not. Three subjects (11.5%) with complete remission, five subjects (19.2%) with pharmacological remission, and two subjects (7.7%) died.

The remission rate in those with a disease period <12 months was 71.4%, and the early modified Osserman classification was 66.7%. The Fisher's test showed an association between the disease period with p–a value of 0.014 and the modified Osserman classification with a p-value of 0.008 with remission after thymectomy. The other factors, such as age, gender, preoperative plasmapheresis, and histopathology findings, showed a p-value of 1.0, 0.197, 0.628, and 1.0, respectively. No statistical analysis proceeded on the type of surgery and preoperative steroid therapy as all subjects underwent transsternal thymectomy procedures and received preoperative steroid therapy (Table 2).

Table 2. Bivariate analysis of prognostic factors of myasthenia gravis remission after thymectomy

Variable	Frequency	Remission (%)	No remission (%)	p*
Age				
– ≤40 years	14	3 (21,4)	11 (78,6)	0,401
– >40 years	12	5 (41,7)	7 (58,3)	
Gender				
– Female	18	4 (22,2)	14 (77,8)	0,197
– Male	8	4 (50)	4 (50)	
Disease duration				
– ≤12 months	7	5 (71,4)	2 (28,6)	0,014**
– >12 months	19	3 (15,8)	16 (84,2)	
Modified Osserman classification				
– I-II	9	6 (66,7)	3 (33,3)	0,008**
– III-V	17	2 (11,8)	15 (88,2)	
Preoperative plasmapheresis				
– Yes	20	7 (35)	13 (65)	0,628
– No	6	1 (16,7)	5 (83,3)	
Thymus histopathology				
– Thymic hyperplasia	7	2 (28,6)	5 (71,4)	1,0
– Other	19	6 (31,6)	13 (68,4)	

In analyzing the prognostic factors (Table 3), the disease period showed a specificity of 88.9% with a negative predictive value of 84.2%, a likelihood ratio (+) of 5.6, and a likelihood ratio (-) of 0.42. The sensitivity was 62.5%, with a positive predictive value of 71.4%. The modified Osserman classification showed a specificity of 83.2%) with a negative predictive value of 88.2%, a likelihood ratio (+) of 4.5, and a likelihood ratio (-) of 0.3. The sensitivity was 75%, with a positive predictive value of 66.7%.

Table 3. Sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio of prognostic factors of myasthenia gravis remission after thymectomy

	Disease duration	Modified Osserman classification
Sensitivity (%)	62,5	75
Specificity (%)	88,9	83,3
PPV (%)	71,4	66,7
NPV (%)	84,2	88,2
LR (+)	5,6	4,5
LR (-)	0,42	0,3

Notes: PPV = Positive predictive value, NPN = Negative predictive value, LR = Likelihood ratio

Discussion

These study characteristics showed a broad age range from three to 64 years; three subjects of 3–15 years were recorded and found to be paralleled to epidemiological data in Asia, showing those under 15 years are common.[3] In the study, 19 subjects (73.1%) showed a more extended disease period (>12 months), and 17 subjects (65.4%) with the modified Osserman classification categories III-V. These findings differed from other studies abroad, showing a shorter disease period with a lower modified Osserman classification (I-II) class.[4,5] Our results showed that remission remains low (<50%), which may be associated with our subject's specific characteristics. This finding differed from other studies showing an increasing remission rate with a longer follow-up to ten years.[6] Though some prognostic factors were identified, in this study, only two variables described in the last paragraph showed to be significant. The other factor showed no considerable correlation, age (p = 0.401), and a difference from a previous study showing age is an influencing factor for remission.[7,8] The variation in age distribution and other variables may contribute to confounding. However, in the study, 71.4% of those under 40 showed a longer disease period (>12 months). The gender factor showed different findings from the previous study. We found no association (p = 0.197) with remission after thymectomy, which contradicts other studies showing female dominance.[4,7] Subject characteristics may contribute to the different findings; of female subjects in the study, 61% showed advanced classification, and 66.7% showed disease period >12 months.

The significant factor, namely, the disease period, showed an excellent specificity of 88.9% with a negative predictive value of 84.2% and moderate sensitivity of 62.5% with a positive predictive value of 71.4%, referred to as a prognostic factor. Subjects with a disease period of <12 months showed a positive likelihood ratio of 5.6 and a negative likelihood ratio of 0.3 in those of >12 months. A study showed remission is higher in those with a shorter period between onset to the surgical procedure (<8-12 months).[7] Study by Iwasa showed a higher AchR antibody in the longer period group than in the shorter duration. Furthermore, a study showed that the antibody titers gradually decreased from 6 months to >4 years postoperative.[9] The finding is presumed to explain higher remission rates after thymectomy in groups with shorter disease periods.

The modified Osserman classification in the study showed a good specificity of 83.2% with a negative predictive value of 88.2% and moderate sensitivity of 75% with a positive predictive value of 66.7%, referred to as a prognostic factor for remission after thymectomy. Those in the lower category of the modified Osserman classification (class I-II) showed a positive likelihood ratio of 4.5 and a negative likelihood ratio of 0.3 for remission after thymectomy compared to the more advanced category of the modified Osserman classification (class III-V). The finding parallels a study that showed an association between AchR antibody titer and the Osserman classification. Those with a lower category of modified Osserman classification show low antibody titer levels, whereas patients with advanced-category show higher antibody levels.[10] This might explain higher remission rates after thymectomy in those with a lower category of the modified Osserman classification group. In class I, those who underwent surgical procedures with six months onset followed higher remission rates than those who did not.[8] However, in this study, no subject with class I but advanced.

No association between plasmapheresis administration preoperatively in our study with remission after thymectomy. A previous case series showed a clinical improvement in their one-year postoperative evaluation. They reported that three subjects experienced complete remission, while two experienced clinical remission. However, in this study, a low remission rate of 35% was found in subjects administered with preoperative plasmapheresis. Our subject's characteristic – of > 12-month disease period – may be responsible for the different findings.[11] Preoperative steroid therapy was presumably associated with a higher remission after thymectomy. Steroid inhibits the immune activation process (T cell activation and B) cell proliferation which plays a role in

subjects' autoimmune nature. The study compared those administered with high-dose preoperative steroids for four to six weeks to those not given.[12] However, in this study, the subjects were those with category class II-IV of modified Osserman classification class II-IV, thus, receiving preoperative steroids. All subjects in this study proceeded with an extended sternotomy transsternal thymectomy procedure. Transcervical and VATS thymectomy have not been performed in patients with myasthenia gravis in our center. In a recent study, thymic hyperplasia on histopathology finding showed no association with remission after thymectomy. It is because small subjects (26.9%) showed thymic hyperplasia histopathology and found in contrast to other studies showing most histopathology being thymic hyperplasia.[5,4,8]

This article is the first study focused on the prognostic factors of remission after thymectomy for myasthenia gravis at the hospital. Research power exceeding 80%, s study has an adequate sample, including cases of myasthenia gravis who underwent thymectomy for five years, with three years of postoperative follow-up. The finding may be valuable as preliminary data for management and patient education. For educational purposes, the result may be helpful to information not to delay the surgical procedure. However, this study's limitation is a single-center referral with advanced characteristics. These characteristics may contribute to low remission rates after thymectomy. In addition, the loss to follow-up numbers in this study was relatively high (18.6%), despite two variables (i.e., preoperative steroid therapy and type of surgical procedure) being unable to be analyzed in this study since all subjects received equal treatment.

Conclusions

Disease period and modified Osserman classification are prognostic factors for remission after thymectomy in myasthenia gravis. In contrast, known factors such as age, gender, preoperative plasmapheresis, preoperative steroid therapy, type of surgical procedures, and thymic histopathology were not.

Disclosure

The authors declare no conflict of interest.

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Role of authors

Author1 Conceptualization Data curation Formal analysis Funding acquisition Investigation Methodology Project administration Resources Software Supervision Validation Visualization Writing

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