Factors Affecting Generalization of Ocular Myasthenia Gravis in Palembang

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Abstract

Introduction. Ocular myasthenia gravis (OMG) is an autoimmune disease which is characterized by weakness of extraocular muscles, levator palpebrae and orbicularis oculi, resulting in ptosis and binocular diplopia. Nearly all patients present with eyelid and extra ocular muscles involvement. Approximately 30% to 80% of patients with OMG experience a conversion to generalized myasthenia gravis (GMG) within 2 years. There are not only have ptosis and diplopia but also limb weakness, bulbar symptoms, or even respiratory failure. This study was aimed to observe the clinical features of OMG to GMG and risk factors and median time to conversion of OMG to GMG of myasthenia gravis patients in Mohammad Hoesin General Hospital Palembang.

Methods. This study is a cohort retrospective study and the data were collected from the medical records of 91 patients who were registered as myasthenia gravis patients during September 2018 to March 2020. Sosiodemographic and clinical characteristics, including onset of OMG to GMG, history of smoking, presence of thymic abnormalities, and medications received were reviewed retrospectively.

Results. A total of 91 OMG patients were observed in this study with 32 (35.2%) patients converted from ocular myastenia gravis to general myastenia gravis. Median conversion time to GMG was 34 months. Risk factor for conversion cases of OMG to MGG was receiving immunosuppressive agents (Risk: 14.7, 95% CI 4.83, 44.7), thymus hyperplasia (Risk: 3.36, CI 95% 0.33, 33.6), Female (Risk: 2.41, 95% CI 0.94, 6.17), Smoking (Risk: 1.56, 95% CI 0.31, 7.81).

Conclusion. Ptosis was the definitive sign for OMG in this study, with all patients had ptosis, thus it needs the cooperation from neuroophthalmologist and neurologist to diagnose and manage this case. Most of converted case was female and those who receive an immunosuppressive agent therapy.

Keywords. Ocular myasthenia gravis, generalized myasthenia gravis, conversion.
Introduction

Myasthenia gravis (MG) is an autoimmune disease with clinical characteristics of fluctuating muscle weakness due to impaired neuromuscular transmission.1-3 This disease is caused by a decrease in the number of acetylcholine receptors at the neuromuscular junction due to the presence of antibodies that attack acetylcholine receptors or other elements of the postsynaptic membrane.3

The global incidence of MG cases is 5-8 cases per 1 million population, 50% of MG cases are initiated by ocular symptoms.4 There are no racial differences and geographic features of MG cases. MG can also occur in all age groups, although early-onset above 70 years of age is rare. Women are more dominant in experiencing MG than men (3:2).5 Nearly 50% of patients in Asian countries have onset under the age of 50 years.3 Symptoms of ocular myasthenia gravis (MGO) are ptosis and diplopia caused by muscle weakness that occurs.1,5 In addition to physical examination, the diagnosis of MG can be made by examining ice packs, antibodies, and electrophysiological examinations.1,3,4 Reported in 2 years 30%-80% of cases of MGO will be converted to generalized myasthenia gravis (MGG), which is characterized by limb weakness, symptoms in the bulbar system, to respiratory disorders.1,4 In one study in Thailand, reported risk factors for conversion of MGO to MGG were female patients, the onset of MGO in old age, thymic hyperplasia, and smoking history.1-3 This study aims to determine the characteristics of MGO patients, the risk factors for conversion of MGO cases to MGG, and the time of conversion of MGO cases to MGG at Dr. Mohammad Hoesin Palembang.

Methods

This research is a descriptive study with a retrospective cohort approach. The data was obtained from the medical records of patients who were recorded as myasthenia gravis patients in the patient register at the neurology polyclinic, Dr. Mohammad Hoesin Palembang, data was collected from the patient register book that was recorded from September 2018 to December 2019, follow-up data for each patient was then followed up and recorded until follow-up in August 2020. Medical record data included in this study were patients diagnosed as myasthenia gravis, ocular myasthenia gravis and myasthenia gravis according to the Myasthenia Gravis Foundation of America (MGFA) grading.

Data processing was carried out using SPSS 22. The data studied included demographic data, namely gender, age, ptosis, diplopia, involvement of the eye muscles, thymus hyperplasia, smoking
history, methylprednisolone consumption, type of case, and length of follow-up until conversion. Then the risk factor analysis and the median time of conversion were carried out for each risk factor.

**Results**

**Characteristics of myasthenia gravis patients at RSUP Dr. Mohammad Hosein**

During the period September 2018 to December 2019, there were 112 patients diagnosed with Myasthenia gravis. There were 21 patients excluded in this study. The clinical characteristics of Myasthenia gravis patients are gender, age, ptosis, diplopia and impaired eyeball movement.

**Gender**

In this study, the number of myasthenia gravis patients was more in female patients, namely 64 patients (70.3%) than men, 27 patients (29.7%), with a ratio of 2.37:1 between women and men.

| Gender | Total (%) |
|--------|-----------|
| Female | 64 (70.3%) |
| Male   | 27 (29.7%) |
| Total  | 91 (100%)  |

**Age**

Patients were categorized into two groups based on age, namely the age group ≤ 50 years and >50 years. The most myasthenic patients were found at the age of ≤ 50 years, namely 61 patients (67%) and aged >50 years as many as 30 patients (33%), with an age range from 17 years to 70 years.

| Age  | Total (%) |
|------|-----------|
| ≤ 50 | 61 (67%)   |
| >50  | 30 (33%)   |
| Total| 91 (100%)  |
Ptosis and diplopia

All patients included in this study had complaints of ptosis, either in one eye or both eyes. The results showed that most patients experienced ptosis in one eye which was experienced by 50 patients (54.9%) and 41 patients (45.1%) both eyes. In this case of myasthenia gravis, the patient may also complain of double vision or diplopia, wherefrom this study there were only 16 patients (17.6%) who had diplopia. In addition, complaints of impaired eye movement were found in 24 patients (26.4%) out of a total of 91 patients who were included in the study.

Table 3. Types of ptosis, diplopia, and eyeball movement disorders patients with myasthenia gravis

| Characteristics                        | Number (%) |
|----------------------------------------|------------|
| Ptosis                                 |            |
| both eyes                              | 41 (45.1%) |
| One eye                                | 50 (54.9%) |
| Diplopia                               |            |
| Exist                                  | 16 (17.6%) |
| None                                   | 75 (82.4%) |
| Disorders of eyeball movement          |            |
| Exist                                  | 24 (26.4%) |
| None                                   | 67 (73.6%) |
| Total                                  | 91 100%    |

Overview of conversion risk factors

In this study, the risk factor for conversion of MGO to MGG was patients with thymic hyperplasia which was found in 4 patients (4.4%), where the four patients had undergone surgery thymectomy by a thoracic surgeon, smoking history in 13 patients (14.3%), and consumption of methylprednisolone in 33 patients (36.3%).
Table 4. Risk factors for conversion into MGG MGO patient

| Characteristics                  | Number (%)  |
|----------------------------------|-------------|
| hyperplasia of the thymus        |             |
| Exist                            | 4 (4.4%)    |
| None                             | 87 (93.6%)  |
| smoking history                  |             |
| Exist                            | 13 (14.3%)  |
| None                             | 78 (75.7%)  |
| Consumption of methylprednisolone|             |
| Yes                              | 33 (36.3%)  |
| No                               | 58 (63.7%)  |
| Total                            | 91 (100%)   |

Types of cases and conversion time

In this study the types of myasthenia gravis cases were categorized into 3 types of cases, MGO, namely cases where patients diagnosed with MGO did not experience other muscle weakness disorders other than the eye muscles in 47 patients (52.6%), MGG, namely the case that the patient already had a disorder in other muscles besides the eye muscles when he was first diagnosed as a case of myasthenia gravis in 12 patients (13.2%), and cases of conversion of MGO to MGG, namely cases where patients previously diagnosed with myasthenia gravis without signs of muscle weakness other than the ocular muscles were found in 32 patients (35.2%).

Of the 32 cases of conversion of MGO to MGG, the highest conversion time occurred after 24 months of follow-up (75%) since the first patient was diagnosed as ocular myasthenia gravis.

Table 5. Case type and patient conversion time

| Characteristics                  | Frequency  |
|----------------------------------|------------|
| Case                             |            |
| MGO                              | 47 (51.6%) |
| MGG                              | 12 (13.2%) |
| Conversion of MGO to MGG         | 32 (35.2%) |
| Total                            | 91 (100%)  |
| Conversion time                  |            |
| < 24 months                      | 8 (25%)    |
| ≥ 24 months                      | 24 (75%)   |
| Total                            | 32 (100%)  |
Risk factor analysis conversion of ocular myasthenia gravis to myasthenia gravis general

In this study, it was found that patients with a history of taking methylprednisolone had a 14.7x risk of changing MGO cases to MGG, with a value of significance/belief of $p<0.05$ ($p=0.00$) followed by thymic hyperplasia, female gender, and smoking history.

Table 6. Analysis of risk factors for conversion into MGGMGO case

| Characteristics                  | Risk  | 95% CI       | p   |
|----------------------------------|-------|--------------|-----|
| Women                            | 2.41  | 0.94, 6.17   | 0.06|
| Hyperplasia thymus               | 3.36  | 0.33, 33.6   | 0.3 |
| Smoking                          | 1.56  | 0.31, 7.81   | 0.5 |
| methylprednisolone consumption   | 14.7  | 4.83, 44.7   | 0.00|

Time of conversion MGO be MGG

In this study, from an analysis of 32 cases of conversion of MGO to MGG. Where data processing is carried out in 2 stages of processing, the first is to determine the dominant component of each risk factor (for example, patients with a history of consuming methylprednisolone are more at risk of conversion than patients who do not take these drugs) after the conversion risk results are obtained (Table 6). calculating the mean of conversion from MGO to MGG for each of these risk factors.

Table 7. Time of occurrence (in months) convert MGO to MGG.

| Risk factors            | conversion time |
|-------------------------|-----------------|
| General                 | 34              |
| Gender                  |                 |
| Female                  | 33              |
| Male                    | 35              |
| Hyperplasia Thymus      |                 |
| Exist                   | 2               |
| None                    | 35              |
| History Smoke           |                 |
| Yes                     | 37              |
| No                      | 32              |
| Consumption Methylprednisolone |          |
| Yes                     | 38              |
| No                      | 27              |
Myasthenia gravis (MG) is an autoimmune disease with clinical characteristics of muscle weakness to fluctuate due to interference with neuromuscular transmission. This disease is caused by a decrease in the number of acetylcholine receptors at the neuromuscular junction due to the presence of antibodies that attack acetylcholine receptors or other elements of the postsynaptic membrane.\(^{1-3,6}\)

Based on the results of the study, it was found that 64 patients (70.3%) of female sex suffered from myasthenia gravis and 27 patients (29.7%) male gender, this is following global epidemiological data, where patients with myasthenia gravis more in women than men in a ratio of 3:2. In Apinyawasisuk et al's study, the highest incidence of MGO and MGG was found in women (51.4% and 69.4%).\(^1\) From the literature it is said that women have higher levels of antibodies, this is a hormonal effect, especially estrogen that affects immune cells both qualitatively and quantitatively so that it has an impact on the production of cytokines, immunoglobulins and B lymphocyte antibodies.

For age, there were 61 patients (67%) and 30 (33%) aged > 50 years, epidemiologically, early-onset myasthenia gravis was more common in people less than 50 years old. There were no case differences for all age groups in cases of myasthenia gravis, although early-onset above 70 years of age was rare.\(^{7,8}\)

In myasthenia gravis, the initial symptom that occurs is muscle weakness, especially in the extraocular muscles, so it is often referred to as ocular myasthenia gravis (MGO). Ptosis, diplopia and impaired eye movement are symptoms that occur when there is a disturbance in the extraocular muscles. Ptosis was found in all patients in this study, whereas for the ptosis eye, 50 patients had ptosis in one eye and 41 patients in both eyes. Diplopia was found in 16 cases, and impaired eye movement in 24 cases.\(^{9,10}\) This is following the research of Paragallo et al, which showed ptosis as the most common complaint of 71.9%, followed by diplopia and other bulbar symptoms.\(^9\)

In this study, the types of cases are categorized into three types of cases: (1) MGO, namely cases where patients diagnosed with MG impaired muscle weakness other than the muscles of the eye, (2) MGG, namely the case of the patient's interference in other muscle in addition to the eye muscles when first diagnosed as a case of myasthenia gravis, (3) cases of conversion of MGO to MGG, namely cases where patients previously diagnosed with myasthenia gravis without signs of muscle weakness other than the ocular muscles.

There were 47 cases of MGO patients, 12 cases of patients diagnosed with MGG when they first came, and 32 cases of patients who were converted from MGO to MGG. Of the 32 cases of
patients converting MGO to MGG, the median analysis for conversion time was mostly more than 24 months with a total of 24 patients (75%). Previous research stated that the conversion time of MGO to MGG occurred in 2 years. 11

The risk factors found in patients with the conversion of MGO to MGG were gender, thymic hyperplasia, smoking history, and history of taking methylprednisolone.12-14 In this study, it was found that patients with a history of using methylprednisolone had a 14.7x risk of converting MGO to MGG, with a significance/confidence value of p=0.00, followed by thymic hyperplasia with a risk of 3.36 (95% CI 0.33). , 33.6 (p=0.3), female gender with risk 2.41 (95% CI 0.94, 6.17) (p=0.06), and smoking history with risk 1.56 (95% CI 0.31, 7.81) (p= 0.05). The overall conversion time of MGO cases to MGG has a median value of 34 months of follow-up, wherefrom the literature it is said that the average conversion occurs within 24 months.15,16

**Conclusion**

Ptosis was the definitive sign for OMG in this study, with all patients having ptosis, thus it needs collaboration from neuro-ophthalmologist and neurologist to diagnose and manage this case. Most of the converted cases were female and those who received immunosuppressive agent therapy.

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