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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. **Objective:** 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 Dr. 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 convertion cases of OMG to MGG was receiving immunosupressive 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 colaboration from neuroophthalmologist and neurologist to diagnose and manage this case. Most of converted case was female and those who receive an immunosupressive agent therapy.

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease with clinical weakness and fluctuating weakness due to impaired neuromuscular transmission.[1–3] This disease is caused by a decrease in the number of acetylcholine receptors on the neuromuscular junction due to the presence of antibodies that attack acetylcholine receptors or other post-synaptic membrane elements.[3]

The global incidence of MG cases is 5-8 cases per 1 million population, 50% of MG cases originate from ocular symptoms.[4] There are no differences in race and geographic features of MG cases. MG can also occur in all age groups, although early onset beyond 70 years is rare. Women are more dominant in experiencing MG than men (3:2).5 Nearly 50% of patients in Asian countries have an onset under the age of 50 years.[3] Symptoms of myasthenia gravis ocular (MGO) are ptosis and diplopia caused by muscle weakness.[1,5] In addition to physical examination, the diagnosis of MG can be done by examining ice packs, antibodies, and electrophysiological examinations.[1,3,4] Reported that within 2 years 30% -80% of cases of MGO will convert to generalized myasthenia gravis (MGG), which is characterized by limb weakness, symptoms in the bulbar system, to respiratory problems.[1.4] In one study in Thailand, the risk factors for conversion of MGO to MGG were reported in female patients, the

onset of MGO in old age, thymus hyperplasia and a history of smoking.[1–3] This study aims to determine the characteristics of MGO patients, the risk factors for conversion of MGO cases to MGG, and the timing of conversion of MGO cases to MGG at Dr. Mohammad Hoesin Palembang.

2. Methods

This research is a descriptive study with a retrospective cohort approach. Data obtained from the medical records of patients who were registered as myasthenia gravis patients in the patient register at the neurology polyclinic, central general hospital dr. Mohammad Hoesin Palembang, data was collected from the patient register book recorded from September 2018 to December 2019, follow up data for each patient was then followed and recorded until follow-up in August 2020.

Medical record data included in this study were patients diagnosed as myastenia gravis, ocular myastenia gravis and myastenia gravis according to the Myastenia Gravis Foundation of America (MGFA) grading. The exclusion criteria were (1) there were no complaints of ptosis from the beginning of the patient's arrival to the end of follow-up, (2) patients who were not diagnosed with myasthenia gravis, (3) patients with incomplete or missing medical records.

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

3. Results

Characteristics of myasthenia gravis patients at Dr. Mohammad Hosein General Hospital Palembang

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

Gender

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

Table 1. Gender of Myasthenia Gravis Patients

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. Most myasthenia patients were found at ≤ 50 years of age, namely 61 patients (67%) and aged> 50 years as many as 30 patients (33%), with an age range from 17 years to 70 years.

Table 2. Age of Myasthenia Gravis Patients

Age	Total (%)
≤ 50	61 (67%)
> 50	30 (33%)
Total	91 (100%)

Ptosis and diplopia

All patients included in this study had complaints of ptosis, both in one eye and in both eyes. It was found that the most patients experienced ptosis in one eye experienced by 50 patients (54.9%) and both eyes as many as 41 patients (45.1%). In this case of myasthenia gravis, the patient also complained of double vision or diplopia, whereas in this study only 16 patients (17.6%) had diplopia. In addition, complaints in the form of eye movement disorders were found in 24 patients (26.4%) of the total 91 patients enrolled in the study.

Table 3. Types of Ptosis, Diplopia, and Eye Movement Disorders in Myasthenia Gravis Patients

Characteristics		Total (%)
Ptosis	Both eyes	41 (45.1%)
	One eyes	50 (54.9%)
Diplopia	Yes	16 (17.6%)
	No	75 (82.4%)
Eyeball movement disorders	Yes	24 (26.4%)
	No	67 (73.6%)
Total		91 (100%)

Overview of risk factors for conversion

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

Table 4. Risk factors for conversion of MGO patients to MGG

Characteristics		Total (%)
Thymus hyperplasia	Yes	4 (4.4%)
	No	87 (93.6%)
Smoking history	Yes	13 (14.3%)
	No	78 (75.7%)
Take methyl prednisolone	Yes	33 (36.3%)
	No	58 (63.7%)
Total		91 (100%)

Type of case and time of conversion

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

Of the 32 patients with the conversion of MGO to MGG, it was found that the most conversion time occurred after 24 months of follow-up (75%) since the first patient was diagnosed as ocular myastenia gravis.

Table 5. Case types 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	MGO	32 (100%)

Analysis of risk factors for conversion of ocular myasthenia gravis to myasthenia gravis general

In this study, it was found that patients with a history of using methylprednisolone had a 14.7x risk of experiencing a change in cases of MGO to MGG, with a significance value of $p < 0.05$ ($p = 0.00$) followed by thymus hyperplasia, female gender, and history of smoke.

Table 6. Analysis of risk factors for conversion of MGO cases to MGG

Characteristics	Risk	CI 95%	P
Woman	2.41	0.94, 6.17	0.06
Thymic Hyperplasia	3.36	0.33, 33.6	0.3
Smoke	1.56	0.31, 7.81	0.5
Take methylprednisolone	14.7	4.83, 44.7	0.00

Time of occurrence of conversion of MGO to MGG

In this study, from the analysis of 32 cases the conversion of MGO to MGG. Where data processing was carried out with 2 processing stages, first the dominant component of each risk factor was determined (for example, patients with a history of consuming methyl prednisolone were more at risk of conversion than patients who did not take these drugs) after the results of the risk of conversion were obtained (table 6). calculation of the mean value of conversion from MGO to MGG for each of these risk factors.

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

Risk factor		Conversion time
Generally		34
Gender	Female	33
	Male	35
Thymic Hyperplasia	Yes	2
	No	35
Smoking history	Yes	37
	No	32
Take methylprednisolone	Yes	38
	No	27

4. Discussion

Myasthenia gravis (MG) is an autoimmune disease with clinical characteristics of fluctuating muscle weakness due to impaired 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 post-synaptic membrane elements.

Analyzes were performed on 91 patients who met the inclusion and exclusion criteria in this study. Data obtained from the medical records of patients who were recorded as myasthenia gravis patients in the patient register at the neurology clinic, central general hospital dr. Mohammad Hoesin Palembang, data was collected from the register book September 2018 to December 2019, follow up data for each patient was then followed and recorded until follow-up in August 2020.

From the descriptive table of patient characteristics, it was found that 64 patients (70.3%) with female gender had myasthenia gravis and 27 patients (29.7%) were male. women versus men at a ratio of 3: 2. In the study of Apinyawasisuk et al, it was found that the incidence of MGO and MGG was highest in women (51.4% and 69.4%). From the literature it is said that women have higher levels of antibodies, this is a hormonal effect, especially estrogen which 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, it was found that 61 patients (67%) and 30 (33%) aged ≤ 50 years old were> 50 years old. Epidemiologically, the early onset of myasthenia gravis was more common in people less than 50 years old. There was no difference in cases for all age groups in cases of myasthenia gravis, although early onset beyond 70 years was rare.

In myasthenia gravis, the initial symptom that occurs is muscle weakness, especially in the extra ocular muscles, so it is often referred to as ocular myastenia gravis (MGO). Ptosis, diplopia and impaired eye movement are symptoms that appear when the extraocular muscles are affected. Ptosis was found in all patients in this study, whereas for eyes with ptosis, 50 patients had ptosis in one eye and 41 patients in both eyes. Diplopia was found in 16 patients, and eye movement disorders in 24 patients. This is in accordance with the study of Murai et al, which showed ptosis as a complaint at most of 71.9%, followed by diplopia, and other bulbar symptoms.

In this study, the types of cases were categorized into 3 types of cases, (1) MGO, namely cases in which patients diagnosed with MG did not experience other muscle weakness disorders besides the eye muscles, (2) MGG, namely cases where the patient already had other muscle disorders besides the eye muscles were first diagnosed as a case of myasthenia gravis, (3) the case of conversion of MGO to MGG, which is a case where a patient 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 arrived, and 32 cases of patients who converted from MGO to MGG. Of the 32 cases of patients converting MGO to MGG, the mean value of the most conversion time was more than 24 months with a total of 24 patients (75%). Based on the literature, it states that the conversion time of MGO to MGG occurs within 2 years in patients who have not.

The risk factors found in patients converting MGO to MGG were gender, thymus hyperplasia, history of smoking, and history of taking the drug methylprednisolone. In this study, it was found that patients with a history of using the drug methylprednisolone had a risk of 14.7x to experience conversion of MGO to MGG, with a significance value of p = 0.00, followed by thymus hyperplasia with a risk of 3.36 (95% CI 0.33, 33.6) (p = 0.3), the sex of the woman with a risk of 2.41 (95% CI 0.94, 6.17) (p = 0.06), and a history of smoking with a risk of 1.56 (95% CI 0.31, 7.81) (p = 0.05). The results obtained are the same as the research of Apinyawasisuk et al, but different from the research conducted by.

Overall, the time for conversion of MGO cases to MGG has a mean value for 34 months of follow-up, where from the literature it is said that the average

conversion occurs within 24 months. In this study, the calculation of the mean time of conversion of MGO cases to MGG for each risk factor was also carried out. The results were obtained for the risk factors for female gender with a mean value of 33 months, men with a mean value of 35 months, a history of smoking with a mean value of 37 months and no smoking with a mean value of 32 months, a history of taking immunosuppressant drugs (methylprednisolone) with a mean value of 38 months and did not consume 27 months, thymus hyperplasia with a median value of 2 months and without hyperplasia 35 months, for thymus hyperplasia, because only 2 patients were found to have a chest CT scan in the case of patients with MGO converting to MGG from a total of 32 patients, so the data are available for time conversion does not represent the real situation.

5. Conclusion

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

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