# Clinical Profile and Outcome of Myasthenic Crisis In Central Taiwan

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**Abstract**

***Background:*** Myasthenia gravis (MG) is an autoimmune disease caused by antibodies to acetylcholine receptors of the skeletal muscle. Myasthenic crisis (MC) is a complication observed during both early and late stage MG cases. In this study, we examined current treatments and three years outcomes in patients with MG and MC. We also investigated the impact of thymectomy and systemic lupus erythematosus (SLE) in patients with MG and MC.

***Methods:*** In this retrospective study, we reviewed the medical records of all patients admitted to one teaching hospital between January 2006 and December 2014 and identified those for whom discharge diagnosis included the International Classification of Diseases, ninth revision (ICD-9) codes corresponding to MG (358.X, all extensions and all positions).

***Results:*** We identified 29 patients and 49 hospitalizations. Among these patients, the cause for initial hospitalization was MG in 16 cases and MC in 13 cases. Six out of the 16 MG patients were readmitted within 3 years; with 2 of the cases due to MC. Eight of the initial 13 MC patients were readmitted within 3 years, and 6 of the cases due to MC. Among these 15 MC patients, 14 were admitted to the intensive care unit (ICU), and 8 were intubation and put on mechanical ventilators. The median ICU stay was 7 days (3-45). Both MG patients who were also diagnosed with SLE experienced MC. One patient died during the first-time hospitalization, and one patient died during re-hospitalization within 2 years.

***Conclusion:*** Plasma exchange (PE) is the main treatment modality of MC, and most patients in our cohort had a good response. Infection is the most common trigger of MC and a significant cause of death. Despite significant morbidity and mortality in patients with MC, a favorable long-term outcome is possible with intensive treatment.

**Key Words:** myathenia gravis, myasthenic crisis, systemic lupus erythematosus, outcome

*Acta Neurol Taiwan 2016;25:129-135*

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Received February 4, 2016. Revised April 17, 2016.
Accepted August 11, 2016.

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## INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease affecting neuromuscular transmission and is characterized by localized or generalized weakness[1]. The incidence rate is reported as 2.1/100,000 and prevalence rate is 14/100,000 in Taiwan[2]. Myasthenic crisis (MC) is a complication of MG, characterized by the worsening of muscle weakness and respiratory failure that requires invasive or non-invasive mechanical ventilation[3,4]. Approximately 15–20% of MG patients experience MC in their lifetime[5]. Factors that can precipitate MC include infection, fever, aspiration pneumonia, physical stress, inadequate treatment, and drug effects[3,6,7]. The mortality rate of MC has declined from 42% in the early 1960s[3] to 4% in the late 1990s[4]. Plasma exchange (PE), plasmapheresis, and intravenous immunoglobulin (IVIG) are common treatment modalities for MC, and they have substantially improved MC outcomes[4,8-12].

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by the production of various autoantibodies [directed mainly against nuclear antigens and double-stranded (ds)DNA] and impaired T and B cell function accompanied by systemic clinical manifestations[13]. Both SLE and MG occur mainly in young women and are typically characterized by periods of exacerbation and remission with a concomitant production of autoantibodies[13]. Furthermore, the coexistence of SLE and MG has been occasionally reported[14-20]. MG may develop prior to or after the diagnosis of SLE[21]. In addition, SLE may develop in MG patients who have undergone thymectomy[13].

Our current understanding of the clinical outcomes of MG and MC is based mainly on reports from 20–30 years ago or on studies from Western countries[1,4,6,9,10,22]. A study in Taiwan reported that extended thymectomy can improve outcomes in patients with thymolipomatous MG[23]; however, to date, there have been no longitudinal studies investigating precipitating factors, clinical outcomes, and the potential impact of SLE on MG and MC in Taiwan.

In this study, we assessed the 3-year outcomes of MG and MC patients who were hospitalized at a single teaching hospital in central Taiwan. We investigated precipitating factors for MC, mortality, and re-hospitalization rates, and treatment modalities in patients with MG and MC. We also investigated the relationship between SLE and MG and MC.

## METHODS

Data source: In this retrospective study, the clinical information on patients was collected from admissions to a single teaching hospital between January 1, 2006 and December 31, 2014. The hospital is an acute care, 1000-bed teaching hospital in central Taiwan. All patients discharged with a diagnosis corresponding to the International Classification of Diseases, ninth revision (ICD-9) codes for MG (358.X, all extensions and all positions) were carefully reviewed by a neurologist to identify those with MG and/or MC to assess treatment modalities and clinical outcomes and to determine the relationship between MG and SLE. The study was approved by the internal review board (IRB) of the hospital (CYCH-IRB: 104001).

**Definition of MG:**

Patients with MG were clinically diagnosed, and the diagnosis was confirmed by one or both of the following tests: repetitive nerve stimulation and the presence of acetylcholine receptor antibodies. MC was then defined as the presence of respiratory failure requiring intubation with either invasive or non-invasive ventilator support in a patient with MG. Those MG patients who were intubated for respiratory failure due to congestive heart failure, statue epilepticus, or acute respiratory distress syndrome were excluded from the current study.

All patients were evaluated for a number of demographic factors and clinical characteristics, including age, sex, length of hospital stay, co-morbidities, and the time between the initial MG-associated hospitalization and the specific outcome.

**Statistics:**

Statistical analyses to examine the associations between MG and MC were performed using the chi-square or Fisher's exact test for categorical variables and Mann-Whitney U test for continuous parameters such as the cost of treatment and length of stay. MedCalc for Windows (MedCalc software, version 12.3, Ostend, Belgium) was used for all statistical analyses.

## RESULTS

Twenty-nine patients fitting the inclusion criteria were admitted during the study period. The characteristics of the patients are shown in Table 1. The cohort mean age was 53.4 ± 14.6 years (22–82), and 52% (15) were female. There was no significant difference in age at first admission between the MC and the MG groups (57.2 vs 50.3 y, $P = 0.21$). Eighteen patients (10 women, 8 men) were below the age of 60 years, and 11 patients (5 women, 6 men) were above the age of 60. The median length of stay was 8 days, interquartile range (IQR) 5-12 days; it was longer in the MC group 11 (9-19) days than the MG group 5 (2.5-8) days. ( $P < 0.01$). The cost was 144283 (71816-167609) for MC group and 25826 (15112-76178) for MG group. ( $P < 0.01$). Among patients with MC, 53.3% (8/15) had endotracheal intubation, and 1 patient received nasal cannula oxygen therapy.

Twenty-nine patients in this cohort were hospitalized for a total of 49 times. Among these, the first hospitalization was due to MG in 16 patients and MC in 13 patients. Among these 16 MG patients, 6 were readmitted within 3 years, while only 2 of the 16 MG patients were readmitted due to MC. Eight of the 13 MC patients were readmitted within 3 years, and 6 of these readmissions were due to MC (Figure 1). Compared to patients who were initially admitted due to MG, first-time admission due to MC was associated with an increased risk for MC (odds ratio (OR): 6). In the 15 MC patients, 14 were admitted to the intensive care unit (ICU) and 8 of these patients were intubated to be put on the mechanical ventilator. The median ICU stay was 7 (3–45) days.

The precipitating event for the onset of MC was infection in 50% (8/16) of patients (5 pneumonia, 3 urinary tract infection), inadequate treatment/drug withdrawal in 3 patients (18.75%), and electrolyte imbalance in one patient (6.25%). Four patients (25%) developed MC without an identified precipitating factor (Table 2). IVIG was administered to 1 MC patient, while PE was performed in 7 patients. Two patients received PE plus intravenous solucortef (IVSC), 3 patients received IVSC, and 2 patients received high dose oral prednisolone. The response to IVIG, PE, and PE plus IVSC was good. One patient died during hospitalization (Table 3).

**Table1.** Characteristics of patients

| | MG (n=16) | MC (n=13) |
|---|---|---|
| Sex | | |
| Men | 8 | 6 |
| Women | 8 | 7 |
| Age | 50.31±15.33 | 57.23±13.29 |
| Thymoma | 6 | 0 |
| Benign | 4 | 0 |
| Malignant | 2 | 0 |
| Thymectomy | 8 | 2 |
| Hyperplasia | 6 | 2 |
| Benign | 2 | 0 |
| Malignant | 2 | 0 |
| MG years | Median 3 mo | Median 2 year |
| Type of MG | | |
| Ocular | 6 | 0 |
| Generalized | 10 | 13 |
| LOS (Median, IQR) | 5 (2.5-8) | 11 (9-19) |
| Cost (Median, IQR) NT | 25826 (15112-76178) | 144283(71816-167609) |
| mortality | 1 | 1 |

MG: myasthenia gravis, MC: myasthenic crisis, IQR:interquartile range,
LOS: Length of stay, NT: Taiwan dollars, 1 USD=32.4 NT.

**Table2.** Co-morbidity of Myasthenia gravis patients

| Co-morbidity | MG (13) | MC (16) | P |
|---|---|---|---|
| DM | 2 | 3 | 1 |
| Hypertension | 4 | 8 | 0.45 |
| Hyperlipidemia | 1 | 2 | 1 |
| Hepatitis | 2 | 1 | 0.57 |
| SLE | 0 | 2 | 0.48 |
| AID | 1 | 0 | 0.44 |
| Infection | 0 | 8 | 0.003 |
| Cancer | 0 | 2 | 1 |
| Asthma | 1 | 0 | 0.44 |
| Heart disease | 1 | 1 | 1 |
| Electrolyte imbalance | 0 | 3 | 0.23 |
| stroke | 0 | 2 | 0.48 |
| No | 7 | 1 | 0.009 |

DM: diabetic mellitus; SLE: Systemic lupus erythematosus; AID: autoimmune disease

**Table 3.** Demographic profile of patients with myasthenic crisis

| Age | Sex | MG Ys | SLE | Thymectomy | Hepatitis | DM | PE | HTN | Solu | IVIG | Re-ad | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 52 | F | 3 | N | 0 | Y | N | 0 | N | 0 | 1 | 0 | Independent |
| 64 | M | 4 | N | 0 | N | Y | 1 | Y | 0 | 0 | 0 | Independent |
| 46 | F | 0.1 | N | 1 | N | N | 0 | N | 1 | 0 | 1 | Independent |
| 42 | F | 0 | Y | 0 | N | N | 0 | N | 1 | 0 | 1 | Independent |
| 68 | M | 7 | N | 0 | N | Y | 0 | Y | 1 | 0 | 0 | Independent |
| 71 | M | 0 | N | 0 | N | N | 1 | Y | 0 | 0 | 0 | Independent |
| 48 | M | 10 | N | 1 | N | N | 1 | N | 0 | 0 | 1 | mortality |
| 63 | M | 1 | N | 0 | N | N | 1 | Y | 0 | 0 | 0 | Independent |
| 53 | F | 8 | Y | 0 | Y | N | 1 | N | 1 | 0 | 4 | Independent |
| 32 | F | 0 | N | 0 | N | N | 0 | N | 1 | 0 | 0 | Independent |
| 61 | M | 2 | N | 0 | N | N | 0 | Y | 0 | 0 | 1 | Independent |
| 63 | F | 1 | N | 0 | N | N | 1 | N | 1 | 0 | 1 | Independent |
| 81 | F | 0.4 | N | 0 | N | N | 1 | N | 1 | 0 | 0 | Independent |
| 70 | F | 0 | N | 0 | N | Y | 1 | Y | 0 | 0 | 0 | Independent |
| 82 | F | 1 | N | 0 | N | N | 1 | Y | 0 | 0 | 0 | mortality |

**Cause of death**

Two patients died within 2 years after the first hospitalization and one patient died 4 years after the first hospitalization.

The first patient, a 48-year-old man previously diagnosed with MG, had undergone thymectomy 10 years ago. Upon admission to the hospital due to MC, the patient was intubated and PE was performed. However, his condition did not improve, and he died 172 days after hospitalization due to pneumonia.

The second patient, an 82-year-old woman who was first hospitalized due to MG, was readmitted 15 months later due to MC. She later died due to the acute exacerbation of chronic obstructive pulmonary disease.

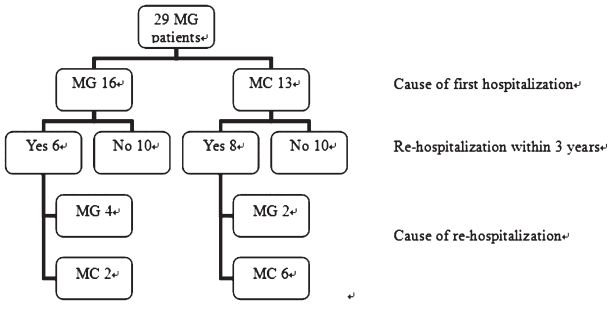
**SLE and MG**

Two MG patients also had SLE, and both developed MC. One of the patients, a 52-year-old woman with a history of SLE of 6 years, was admitted due to MC. After this episode, the patient was readmitted three more times

within the next 2 years, and two of these were due to MC. The patient was independent in her daily activities. The second patient, a 42-year-old woman with a history of SLE of more than 20 years, was diagnosed with MG 2 years before her admission to the hospital due to MC. She received thymectomy 9 months later, and her condition improved with full muscle strength postoperatively. In comparison to patients without SLE, in SLE/MG patients, there have higher risks of MC (OR: 4.65).

**Thymoma and MG**

In this study, thymoma was diagnosed in 6 patients, 4 of whom underwent thymectomy, and 2 patients had malignant thymoma, 2 were diagnosed by chest computed tomography. Ten patients received thymectomy, 4 of the 8 patients were diagnosed with thymoma, and 6 of the patients had thymus hyperplasia. Both patients with malignant thymoma did not experience MC. Two of the 10 patients (20%) received thymectomy experienced MC, while 11 (57.9%) of the 19 patients who did not undergo thymectomy experienced MC. The risk for MC in patients who did not undergo thymectomy was higher than that in patients who underwent thymectomy (OR: 5.5). The presence of a thymoma did not increase the risk for MC, and the risk for MC was decreased in patients who underwent thymectomy.




MG: myasthenia gravis, MC: myasthenic crisis

**Figure 1.** Flow chart of Myasthenia gravis patients

## DISCUSSION

The prevalence of MG is higher in women than in men, with the sex ratio of approximately 2 to 1 (W: M) [2,24]. Previous studies have found a higher incidence of admission due to MG in women with MG than in men with MG during the first six decades of life, while the incidence of admission appears to be more frequent in men during the subsequent three decades.1 However, one study has reported that the incidence of admission is equal between men and women[25]. In our study, among those admitted to our hospital, there were no sex differences between the 18 patients who were below the age of 60 years (10 women, 8 men) or the eleven patients who were above the age of 60 years (5 women, 6 men). Our results, which are in agreement with the findings of Poulas et al., may be due to the enrolment of only those patients who were admitted to the hospital for the first time, as well as the relatively small number of patients included in the cohort.

PE and IVIG are commonly used for the treatment of MC[1,3,4,10]. Previous studies have shown that the efficacy of IVIG and PE in the treatment of MC are not significantly different[26]. However, one study suggests that PE is more effective than IVIG[3]. In our study, 4 of the 15 patients with MG received IVSC, 6 patients received only PE, 3 patients received PE and IVSC, 1 patient received IVIG, and none of the patients received plasmapheresis. One reason for the high number of patients receiving PE may be the policies of the national health insurance system. Importantly, all patients had a good response to treatment, suggesting that PE is a suitable choice of treatment.

Both SLE and MG are autoimmune diseases, and their co-occurrence has been well documented. Previous studies have reported that the co-occurrence of SLE and MG may increase the risk of MC[27]. The prevalence of SLE among MG patients was reported to be approximately 7.7%[28]. In our study, 2 MG patients (6.9%) had SLE in agreement with the previous report. Both of these patients experienced MC during first admission, and both were readmitted due to MC. Further investigation is needed to determine whether the co-occurrence of SLE and MG increases the risk of recurrent MC.

It has been previously reported that SLE may appear following thymectomy. Thymectomy is considered as a precipitating factor for autoimmune diseases, including SLE[13,29]. However, neither of the SLE patients had a history of thymectomy, while none of the 10 patients who underwent thymectomy developed SLE. The difference might be related to the relatively short follow-up period in our study, because SLE may appear 13 years after

thymectomy[13].

The most common event to trigger an MC is infection, which accounts for 50% of MC episodes; inadequate treatment or drug withdrawal are other major precipitating events. The results of our study are the same as those found by Sharma et al., who showed that 50% of MC cases were related to infection and 30% were related to inadequate treatment or drug withdrawal[22]. Similar to the previous study by Sharma et al., no precipitating factors could be found in approximately 30–40% of the MC patients. In this study, no precipitating factors were found in 25% of the patients[4]. Our study also found that a patient's first-time admission due to MC increased the risk of recurrent MC; however, this did not reach statistical significance, likely due to the relatively small number of patients. These results highlight the importance of infection prevention and adherence to regular treatment in the prevention of MC.

As Soleimeni et al. have reported, 30 our study also showed that the risk of MC was higher in patients who did not undergo thymectomy than the MC risk in patients who underwent thymectomy with an OR of 5.5.

Approximately two-thirds to 90% of the MC patients require intubation and mechanical ventilation. In this study, 53.3% of MC patients received intubation. The length of hospital stay for MC patients in our study was longer than the report in the study of United States of America (U.S.A.)[1], but shorter than the report in the study of India[22]. The difference may be related to patient selection. The U.S.A study is a national database study, and the Indian study included patients from a tertiary care teaching hospital. Our study was performed in a community teaching hospital.

Conclusion: Infection is the most common precipitating factor for MC and is an important cause of death in MC. PE is a suitable treatment for MC. Most cases of MC can have favorable outcomes if treatment is implemented on time.

There are several limitations in our study. First, this is a retrospective study with a small number of patients. In addition, this study was conducted at a single hospital. Finally, we did not determine the levels of antinuclear (ANA) and anti-ds-DNA autoantibodies, or the anti-tetanus toxin (TT) antibody in patients, which might have led to the underestimation of patients with SLE.

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