Predictors of extubation outcomes following myasthenic crisis

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Abstract

Objective: Myasthenic crisis (MC) is considered the most severe adverse event in patients with myasthenia gravis. The present retrospective study was performed to evaluate the predictors of clinical outcomes in patients with MC.

Methods: The medical charts of 33 patients (19 women, 14 men) with 76 MC attacks from 2002 to 2014 were retrospectively reviewed. Early extubation (≤7 days) and prolonged ventilation (>15 days) during the MC were used to assess patient outcomes.

Results: Among the 33 patients, 24 (72.7%) had positive acetylcholine receptor antibody test results and 20 (60.6%) experienced recurrent MC attacks (>2 episodes) during follow-up (median 83.6 months, range 1.5–177 months). Plasma exchange during an MC was significantly associated with early extubation. Male sex, older age (>50 years), atelectasis, and ventilator-associated pneumonia significantly contributed to prolonged ventilation. In 22 patients who underwent thymectomy, both the duration between MC attacks and the mean number of MC attacks were significantly reduced after surgery.

Conclusions: Plasma exchange during MC attacks was found to be important for early extubation; older patients and those with atelectasis or ventilator-associated pneumonia were more vulnerable to prolonged ventilation. Thymectomy may be useful to prevent recurrence of MC.

Keywords
Myasthenia gravis, myasthenic crisis, early extubation, thymectomy, plasma exchange, prolonged ventilation, surgery

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Introduction

Myasthenia gravis (MG) is an autoimmune disease caused by antibodies to acetylcholine receptors on the postsynaptic motor end-plate in the neuromuscular junction, leading to generalized or localized muscle weakness.\(^1\,^2\) Myasthenic crisis (MC) is a severe presentation of MG in which patients experience a rapid deterioration of muscle control. In its most severe form, MC leads to paralysis of the respiratory or upper airway muscles, resulting in respiratory failure that requires mechanical ventilation and intensive care unit management.\(^2\,^3\) MC is considered the most severe life-threatening but reversible neurological emergency in patients with MG. The lifetime prevalence of MC in patients with MG ranges from 20% to 30% and most frequently occurs within the first year of illness.\(^3\,^5\)

An MC can result from many different aetiologies, including respiratory tract infections, drug abuse, electrolyte imbalances, or other unidentifiable factors.\(^2\,^3\,^6\) The management of MC is challenging because of its fluctuant nature.\(^7\,^9\) With improvement in respiratory care and intensive care unit management, the MC-associated mortality rate has declined from >40% in the early 1960s to approximately 5% today.\(^2\,^5\) Immunologic therapies, including plasma exchange (PE), intravenous immunoglobulin (IVIG), and corticosteroids, are considered the mainstays of treatment during an MC; however, no consensus or standardized management for these patients has been established.\(^2\,^4\,^7\) Additionally, thymus dysfunction is pathogenically linked to MG, and thymectomy has been widely performed as part of the treatment of general MG. However, little is known about the influence of thymectomy on MC attacks. Therefore, the present retrospective chart review was performed to evaluate 33 patients with 76 episodes of MC at the Myasthenia Gravis Research Center of the First Affiliated Hospital of Sun Yat-sen University, China from 2002 to 2014. In this cohort of Chinese patients, the authors analysed potential factors affecting the outcomes of MC and studied the potential relationship between thymectomy and MC attacks.

Patients and methods

Patients

The medical charts of 33 Chinese patients with MG with a history of MC diagnosed and treated from May 2002 to December 2014 at the Myasthenia Gravis Research Center of the First Affiliated Hospital of Sun Yat-sen University were retrospectively reviewed. This retrospective study was approved by the Ethics Committee and Institutional Review Board of the First Affiliated Hospital of Sun Yat-sen University. MG was diagnosed by experienced neurologists using previously reported standard diagnostic criteria.\(^10\) MC was defined as a rapid deterioration of MG characterized by neuromuscular respiratory failure requiring ventilator support and airway protection.\(^11\) Patients with MG undergoing a surgical procedure requiring intubation and who experienced delayed extubation of >24 h after the procedure were also considered to have experienced an MC.\(^4\,^6\) Long-term follow-up was continued through outpatient clinic visits or telephone interviews, and the interval between two consecutive follow-up visits was <6 months.

Treatments

A multidisciplinary protocol was required for the management of MC.\(^2\,^12\) Experienced intensive care unit neurologists managed the patients and their complications with a combination of general critical care treatment, respiratory support (intubation and mechanical ventilation, noninvasive positive-pressure ventilation), and medications...
including cholinesterase inhibitors and specific immunotherapies (e.g., PE, IVIG, corticosteroid treatment). All patients initially underwent standard intubation and mechanical ventilation; tracheostomy was performed when the duration of intubation was ≥2 weeks. Typically, guidelines for extubation in patients without MG include a vital capacity of ≥15 ml/kg, maximal inspiratory pressure of ≤−20 cm H₂O, expiratory pressure of >40 cm H₂O, and tidal volume of ≥5 ml/kg. However, there is a lack of clinical criteria for when and how to safely extubate patients with MG because of their tendency to develop fluctuating weakness and pulmonary complications. Therefore, the decision to extubate patients with MG relies mostly on the clinical judgment of the intensive care unit neurologist.

**Clinical responses**

The duration of ventilation during an MC is an important indicator of treatment efficacy. In the present study, early extubation and prolonged ventilation were considered the primary outcome measures. Early extubation was defined as intubation and ventilation support for <7 days; prolonged ventilation was defined as the requirement for mechanical ventilation for >15 days. For patients with MG who underwent thymectomy, the severity and frequency of MC before and after thymectomy were also evaluated during the long-term follow-up.

**Statistical analysis**

Statistical analysis was performed with SPSS 18.0 software (IBM, Armonk, NY, USA). Continuous variables are presented as median with interquartile range. Categorical data are presented as counts and proportions. Categorical variables were compared by the chi-square test or Fisher’s exact test. Paired variables in Table 5 were analysed by the paired McNemar test. The duration of intubation during MC attacks was evaluated by Kaplan–Meier analysis using the Wilcoxon test. Statistical significance was set at \( P < 0.05 \).

**Results**

**Patient profile**

Thirty-three patients with MG (19 women, 14 men) with 76 documented episodes of MC managed at the Myasthenia Gravis Research Center were included in the analysis. The median age at MG onset was 33 years (range 2.8 – 75 years), and the median interval from disease onset to first MC was 6 months (range 0.5 – 60 months). Twenty-two patients (66.7%) underwent thymectomy. Eight patients (24.2%) were diagnosed with concurrent thymoma. Twenty-four patients (72.7%) were acetylcholine receptor antibody-positive. The main comorbid diseases were hyperthyroidism (4 patients), hypertension (2 patients), and pulmonary tuberculosis (2 patients). The characteristics of the study cohort are summarized in Table 1. Within the follow-up period (median 83.6, range 1.5 – 177 months), 20 of 33 patients (60.6%) experienced recurrent MCs (≥2 episodes).

**Early extubation and prolonged ventilation**

Early extubation (ventilation of ≤7 days) and prolonged ventilation (ventilation of >15 days) were evaluated as outcome measures, and the potential risk factors affecting these outcomes in patients with MC were assessed. First, the outcomes following each patient’s first MC were analysed. The following variables were included in the analysis: sex, age at the time of MC onset, comorbid hyperthyroidism, any identifiable triggers of MC, immunotherapies administered for treatment, atelectasis, and ventilator-associated pneumonia (VAP). Using univariate analysis, patients who underwent
early PE were more likely to be successfully extubated early \((P = 0.049)\). There were no differences among the use of PE, IVIG, or corticosteroid treatments in patients with prolonged ventilation. Male sex \((P = 0.047)\), an age of >50 years \((P = 0.023)\), atelectasis \((P = 0.008)\), and VAP \((P = 0.004)\) occurred significantly more frequently in patients with prolonged ventilation. Identifiable causes of MC and the anti-acetylcholine receptor antibody status were not associated with early extubation or prolonged ventilation. These results are summarized in Tables 2 and 3. The results of a comparison of patients in the early extubation group \((n = 11)\) and prolonged extubation group \((n = 8)\) were consistent with the above-described conclusion: younger female patients with PE tended to undergo successful early extubation, while older male patients with atelectasis or VAP tended to have poor outcomes (Table 4). In an effort to determine whether the role of PE during the first MC attack of each patient with MG could be generalized to other types of MC, 55 episodes of MC were analysed \((n = 28)\) for early extubation, \(n = 27\) for prolonged extubation; the results also showed that PE might contribute to successful early extubation (Supplementary Table 1). Furthermore, Kaplan–Meier analysis using the Wilcoxon test revealed that male sex \((P = 0.024)\), atelectasis \((P = 0.013)\), and VAP \((P < 0.001)\) were associated with prolonged ventilation, and the use of PE \((P = 0.068)\) seemed to be a good predictor of early extubation (Figure 1).

**Thymectomy and MC attacks**

The relationship between thymectomy and MC in patients with MG undergoing surgical treatment is shown in Table 5. The severity of MC, including the duration of ventilation, rate of early extubation, and prolonged ventilation, was analysed in these patients. There was no difference in the duration of ventilation between patients who developed MC before and after thymectomy. Additionally, patients who underwent thymectomy had significantly fewer MC episodes \((P = 0.016)\) and a longer duration between MC attacks (median, 46 vs. 9 months, \(P = 0.036\)) than did patients who did not undergo thymectomy. Therefore, thymectomy seemed to be associated with a decreased risk of MC recurrence but not severity.

**Discussion**

Myasthenia gravis is a rare disease with an estimated prevalence of 5 to 15 per 100 000 individuals. Of those diagnosed with MG, 20% to 30% will experience an MC.\(^3\)\(^-\)\(^5\),\(^1\)\(^4\) Although an MC is a severe, life-threatening event in patients with MG, few prospective studies on MCs in large cohorts have been performed. The current understanding of
the clinical course, complications, treatments, and outcomes of MC is mostly based on retrospective reports. Therefore, the present retrospective study of a relatively large cohort of Chinese patients with MG and a history of MC was performed to further investigate this life-threatening disease. The study showed that 33.3% of patients with MC achieved early extubation (≤7 days), and only 24.2% of patients needed prolonged ventilation (>15 days). Treatment with PE ($P = 0.049$)

| Table 2. Analysis of potential factors affecting early extubation (≤7 days) during a myasthenic crisis. |
|-------------------------------------------------|-------------------------------------------------|-------------------|
| Variables                                      | Ventilation ≤7 days n = 11 (33.3%) | Ventilation >7 days n = 22 (66.7%) | $P$-value* |
| Sex                                            |                                   |                                 | 0.105      |
| Male                                           | 14                                 | 2 (18.2)                        | 12 (54.5)  |
| Female                                         | 19                                 | 9 (81.8)                        | 10 (45.5)  |
| Age at MC onset                                |                                   |                                 | 0.141      |
| ≤50 years                                      | 23                                 | 10 (90.9)                       | 13 (59.1)  |
| >50 years                                      | 10                                 | 1 (9.1)                         | 9 (40.9)   |
| Comorbid hyperthyroidism                       |                                   |                                 | 0.586      |
| Yes                                            | 4                                  | 2 (18.2)                        | 2 (9.1)    |
| No                                             | 29                                 | 9 (81.8)                        | 20 (90.9)  |
| Causes of MC                                   |                                   |                                 | 0.903      |
| Pulmonary infectious                           | 20                                 | 6 (54.5)                        | 14 (63.6)  |
| DRPS                                           | 6                                  | 2 (18.2)                        | 4 (18.2)   |
| Electrolyte imbalance                          | 3                                  | 1 (9.1)                         | 2 (9.1)    |
| Unknown                                        | 4                                  | 2 (18.2)                        | 2 (9.1)    |
| Treatment during MC                            |                                   |                                 | 0.049      |
| Plasma exchange                                |                                   |                                 |            |
| Yes                                            | 16                                 | 8 (72.7)                        | 8 (36.4)   |
| No                                             | 17                                 | 3 (27.3)                        | 14 (63.6)  |
| IVIG                                           |                                   |                                 | 0.794      |
| Yes                                            | 22                                 | 7 (63.6)                        | 15 (68.2)  |
| No                                             | 11                                 | 4 (36.4)                        | 7 (31.8)   |
| Corticosteroid                                 |                                   |                                 | 1.000      |
| Yes                                            | 24                                 | 8 (72.7)                        | 16 (72.7)  |
| No                                             | 9                                  | 3 (27.3)                        | 6 (27.3)   |
| Atelectasis                                    |                                   |                                 | 0.143      |
| Yes                                            | 5                                  | 0 (0.0)                         | 5 (22.7)   |
| No                                             | 28                                 | 11 (100.0)                      | 17 (77.3)  |
| Ventilator-associated pneumonia                |                                   |                                 | 0.026      |
| Yes                                            | 18                                 | 3 (27.3)                        | 15 (68.2)  |
| No                                             | 15                                 | 8 (72.7)                        | 7 (31.8)   |
| Anti-AchR antibody status                      |                                   |                                 | 1.000      |
| Positive                                       | 24                                 | 8 (72.7)                        | 16 (72.7)  |
| Negative                                       | 9                                  | 3 (27.3)                        | 6 (27.3)   |

Data are presented as n (%).
Pulmonary infections included aspiration pneumonitis, bacterial pneumonia, and nonspecific upper respiratory infection.
MC, myasthenic crisis; IVIG, intravenous immunoglobulin; DRPS, drug-related problems, including discretionary or non-prescribed drug withdrawal or administration; AchR, acetylcholine receptor.
*Chi-square test.

the clinical course, complications, treatments, and outcomes of MC is mostly based on retrospective reports. Therefore, the present retrospective study of a relatively large cohort of Chinese patients with MG and a history of MC was performed to further investigate this life-threatening disease. The study showed that 33.3% of patients with MC achieved early extubation (≤7 days), and only 24.2% of patients needed prolonged ventilation (>15 days). Treatment with PE ($P = 0.049$)
Table 3. Analysis of potential factors affecting prolonged ventilation (>15 days) in patients with a myasthenic crisis.

| Variables                          | No. | Ventilation ≤15 days (n = 25, 75.8%) | Ventilation >15 days (n = 8, 24.2%) | P-value* |
|-----------------------------------|-----|------------------------------------|-----------------------------------|----------|
| Sex                               |     |                                    |                                   | 0.047    |
| Male                              | 14  | 8 (32.0)                           | 6 (75.0)                          |          |
| Female                            | 19  | 17 (68.0)                          | 2 (25.0)                          |          |
| Age at MC onset                   |     |                                    |                                   | 0.023    |
| ≤50 years                         | 23  | 20 (80.0)                          | 3 (37.5)                          |          |
| >50 years                         | 10  | 5 (20.0)                           | 5 (62.5)                          |          |
| Comorbid hyperthyroidism          |     |                                    |                                   | 1.000    |
| Yes                               | 4   | 3 (13.6)                           | 1 (12.5)                          |          |
| No                                | 29  | 22 (86.4)                          | 7 (87.5)                          |          |
| Causes of MC                      |     |                                    |                                   | 0.954    |
| Pulmonary infectious              | 20  | 15 (60.0)                          | 5 (62.5)                          |          |
| DRPS                              | 6   | 5 (20.0)                           | 1 (12.5)                          |          |
| Electrolyte metabolism imbalance  | 3   | 2 (8.0)                            | 1 (12.5)                          |          |
| Unknown                           | 4   | 3 (12.0)                           | 1 (12.5)                          |          |
| Treatment during MC              |     |                                    |                                   | 0.225    |
| Plasma exchange                   |     |                                    |                                   |          |
| Yes                               | 16  | 14 (56.0)                          | 2 (25.0)                          |          |
| No                                | 17  | 11 (44.0)                          | 6 (75.0)                          |          |
| IVIG                              |     |                                    |                                   | 0.315    |
| Yes                               | 22  | 15 (60.0)                          | 7 (87.5)                          |          |
| No                                | 11  | 10 (40.0)                          | 1 (12.5)                          |          |
| Corticosteroid                    |     |                                    |                                   | 1.000    |
| Yes                               | 24  | 18 (72.0)                          | 6 (75.0)                          |          |
| No                                | 9   | 7 (28.0)                           | 2 (25.0)                          |          |
| Atelectasis                       |     |                                    |                                   | 0.008    |
| Yes                               | 5   | 1 (4.0)                            | 4 (50.0)                          |          |
| No                                | 28  | 24 (96.0)                          | 4 (50.0)                          |          |
| Ventilator-associated pneumonia   |     |                                    |                                   | 0.004    |
| Yes                               | 18  | 10 (40.0)                          | 8 (100.0)                         |          |
| No                                | 15  | 15 (60.0)                          | 0 (0.0)                           |          |
| Anti-AchR antibody status         |     |                                    |                                   | 0.229    |
| Positive                          | 24  | 20 (80.0)                          | 4 (50.0)                          |          |
| Negative                          | 9   | 5 (20.0)                           | 4 (50.0)                          |          |

Data are presented as n (%).
Pulmonary infections included aspiration pneumonitis, bacterial pneumonia, and nonspecific upper respiratory infection. MC, myasthenic crisis; IVIG, intravenous immunoglobulin; DRPS, drug-related problems, including discretionary or non-prescribed drug withdrawal or administration. AchR, acetylcholine receptor.

*Chi-square test.

may be useful for early extubation. However, male sex (P = 0.047), age of >50 years (P = 0.023), atelectasis (P = 0.008), and VAP (P = 0.004) were significantly associated with prolonged ventilation. This conclusion was further confirmed by comparison between patients in the early extubation group (n = 11) and prolonged
extubation group (n = 8). In addition, there was evidence that thymectomy may be related to a reduction in MC recurrence.

Plasma exchange and IVIG are often used during an MC. However, because of the lack of evidence and clinical consensus, the choice of which immunomodulating treatment to use relies on the judgment of the treating physician.\textsuperscript{2,7,12,17–19} The present study showed that PE is an effective treatment for MC. The use of PE was associated with a significantly higher rate of early

| Table 4. Potential factors affecting ventilation time (≤7 or >15 days) in patients with a myasthenic crisis. |
|---|---|---|---|
| Variables | No. | Ventilation ≤7 days (n = 11) | Ventilation >15 days (n = 8) | P-value* |
| Sex | | | | 0.024 |
| Male | 8 | 2 (25.0) | 6 (75.0) | |
| Female | 11 | 9 (81.8) | 2 (18.2) | |
| Age at MC onset | | | | 0.041 |
| ≤50 years | 13 | 10 (76.9) | 3 (23.1) | |
| >50 years | 6 | 1 (16.7) | 5 (83.3) | |
| Comorbid hyperthyroidism | | | | 1.000 |
| Yes | 3 | 1 (66.7) | 1 (33.3) | |
| No | 16 | 9 (56.2) | 7 (43.8) | |
| Causes of MC | | | | 0.961 |
| Pulmonary infectious | 11 | 6 (54.5) | 5 (45.5) | |
| DRPS | 3 | 2 (66.7) | 1 (33.3) | |
| Electrolyte metabolism imbalance | 2 | 1 (50.0) | 1 (50.0) | |
| Unknown | 3 | 2 (66.7) | 1 (33.3) | |
| Treatment during MC | | | | 0.070 |
| Plasma exchange | | | | |
| Yes | 10 | 8 (80.0) | 2 (20.0) | |
| No | 9 | 3 (33.3) | 6 (66.7) | |
| IVIG | | | | 0.338 |
| Yes | 14 | 7 (50.0) | 7 (50.0) | |
| No | 5 | 4 (80.0) | 1 (20.0) | |
| Corticosteroid | | | | 1.000 |
| Yes | 14 | 8 (57.1) | 6 (42.9) | |
| No | 5 | 3 (60.0) | 2 (40.0) | |
| Atelectasis | | | | 0.018 |
| Yes | 4 | 0 (0.0) | 4 (100.0) | |
| No | 15 | 11 (73.3) | 4 (26.7) | |
| Ventilator-associated pneumonia | | | | 0.003 |
| Yes | 11 | 3 (27.3) | 8 (72.7) | |
| No | 8 | 8 (100.0) | 0 (0.0) | |
| Anti-AchR antibody status | | | | 0.377 |
| Positive | 12 | 8 (66.7) | 4 (33.3) | |
| Negative | 7 | 3 (42.9) | 4 (57.1) | |

Data are presented as n (%).
Pulmonary infections included aspiration pneumonitis, bacterial pneumonia, and nonspecific upper respiratory infection.
MC, myasthenic crisis; IVIG, intravenous immunoglobulin; DRPS: drug-related problems, including discretionary or non-prescribed drug withdrawal or administration; AchR, acetylcholine receptor.

*Fisher’s exact test.
Figure 1. Kaplan–Meier curves of extubation in patients with myasthenia gravis during a myasthenic crisis. (a) The use of plasma exchange during each crisis seemed to positively contribute to early extubation. (b) Male sex, (c) ventilator-associated pneumonia, and (d) atelectasis after intubation were significantly associated with delayed extubation. A $P$-value of $<0.05$ was considered statistically significant.

Table 5. Relationship between thymectomy and myasthenic crisis in patients with myasthenia gravis undergoing surgical treatment.

| Variables                      | MCBT     | MCAT     | $P$-value$^*$ |
|--------------------------------|----------|----------|---------------|
| Severity of MC                 |          |          |               |
| Days of ventilation, median (IQR) | 8 (5–14) | 5 (3–12) | 0.140         |
| Early extubation, ≤7 days (n)  | 7        | 10       | 0.453         |
| Prolonged ventilation, >15 days (n) | 3        | 2        | 1.000         |
| Frequency of MC                |          |          |               |
| Months between MC attacks (mean, range) | 9 (7–24) | 46 (11.6–61.7) | 0.036         |
| Number of episodes, mean (range) | 1 (1–3)  | 1 (1–1)  | 0.016         |
| Number of episodes, total (range) | 29 (1–6) | 17 (1–2) | –             |

MCBT, myasthenic crisis before thymectomy; MCAT, myasthenic crisis after thymectomy.

$^*$Paired variables were analysed by the paired McNemar test.
extubation, whereas the use of IVIG was not significant. As demonstrated in previous studies, PE can rapidly eliminate the pathological autoantibodies that lead to the phenotypic expression of MG.20 The mechanism by which IVIG acts is less clear, and it may take longer for IVIG to reach its maximal effect.21-23 However, further clarification with randomized controlled clinical trials is needed.

Respiratory complications often affect the prognosis of MC,2,12,24 In the present cohort, VAP occurred in 18 of 33 (54.5%) patients and was an independent adverse prognostic factor for early extubation ($P = 0.026$). In previous reports, VAP was common and identified as a main cause of prolonged intubation or reintubation during MC.24 Strategies aimed at preventing VAP are needed to improve MC therapy and allow for early extubation. Interventions that reportedly prevent VAP include suction, intermittent positive-pressure breathing, bronchodilators, and chest physiotherapy.25 Additionally, five patients (15.2%) in the present study developed pulmonary atelectasis during their MC; atelectasis was significantly associated with prolonged ventilation ($P = 0.008$).

The current study also showed that thymectomy was related to a reduced frequency but not severity of MC. A limited number of studies have reported a relationship between thymectomy and MC.26-28 A study of 20 patients from Iran concluded that thymectomy decreased the rate of MC in patients with non-thymomatous MG.27 Massine et al.26 also reported that thymectomy reduced the rates of MC. However, because of small sample sizes and lack of long-term follow-up, conclusive evidence has not yet been provided. The present study involved a relatively large cohort with a long-term follow-up. Despite the evidence suggesting a relationship between thymectomy and a decreased risk of MC, the retrospective study design does not allow for causal conclusions regarding the association of thymectomy with the risk of MC recurrence and ventilator prognosis.

This study is the first comprehensive analysis of predictors of early extubation and prolonged ventilation during MC in a Chinese cohort. Because of the retrospective and observational nature of the study, the results are subject to limitations. First, as a retrospective analysis, the study is vulnerable to selection bias. Second, various physicians treated and evaluated the patients based on personal clinical judgments. Third, the analysis is limited by the sample size and inability to stratify patients into more specific clinical categories for comparison. Nevertheless, to the best of our knowledge, this is the first cohort of Chinese patients with MC to be studied in aggregate. The results indicate that the use of PE and prevention of VAP and atelectasis are important for early extubation. Thymectomy may be useful for the prevention of MC recurrence, but more research on this topic is required. A multicentre randomized controlled trial is needed to confirm these conclusions.

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**Declaration of conflicting interests**

The authors declare that there is no conflict of interest.

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