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Clinical study

Clinical predictors of steroid-induced exacerbation in myasthenia gravis

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Abstract

Although oral corticosteroids are effective for the treatment of myasthenia gravis (MG), the possibility of steroid-induced exacerbation of symptoms, especially during the initial course of steroid therapy, has limited their use patients with severe MG. However, the factors influencing or predicting in exacerbation are not well understood. The purpose of this study was to identify the clinical factors that predict the initial paradoxical exacerbation of MG in response to steroid therapy. Fifty-five consecutive patients who were administered for the first time high doses of prednisone (40–80 mg) in a tertiary medical centre in Seoul, were included. Prednisone-induced exacerbation was defined as a significant reduction in a patient's Myasthenia Gravis Severity Scale (MSS) score within 4 weeks of prednisone administration. We divided the patients into two groups on the basis of whether or not they experienced prednisone-induced exacerbation, and investigated the differences between the two groups with respect to clinical, laboratory and electrophysiological features. Twenty-three patients (42%) experienced definite exacerbation after prednisone therapy. Older age, predominantly severe bulbar symptoms, and low MSS score were found to be significant clinical predictors of exacerbation by multivariate logistic regression analysis. A high daily dosage of prednisone relative to body weight was found to be neither a predictor of exacerbation nor a predictor of early improvement in bivariate correlation analysis. Steroid-induced exacerbation in MG is a frequently encountered and challenging problem. Clinicians should be aware of the possibility of exacerbation of MG when prescribing prednisone, especially when treating elderly, bulbar dominant, or severely myasthenic patients.

Keywords: Myasthenia gravis; Steroids; Prednisone; Exacerbation; Predictor

1. Introduction

The first immunosuppressive agents used in the treatment of myasthenia gravis (MG) were corticosteroids. Prednisone is the most commonly used agent in the US[1,2] and in our opinion also in Korea (in our opinion). Daily administration of high doses of prednisone frequently results in rapid improvement, often producing a remission of MG. However "paradoxical" exacerbation of MG by prednisone is also a well-known phenomenon, especially during the initial course of therapy.[3–5] The reported frequency of prednisone-induced exacerbation varies between 25% and 75%.[7,11,12] A wide range of severities of exacerbation have also been reported, varying between mild aggravation of weakness to death from respiratory failure.[6,7]

Prednisone is usually used as a secondary agent in combination therapy for MG when symptoms cannot be adequately controlled with anti-cholinesterase agent monotherapy. Accordingly, it is likely that prednisone-induced exacerbation is a frequent problem for clinicians who prescribe prednisone for anti-cholinesterase-resistant MG. Thus, factors that provoke prednisone-induced exacerbation, and methods that can prevent or minimize prednisone-induced exacerbation are topics of great relevance to clinicians. However, until recently no published studies concerning MG have focused on these issues.

The current study was designed to determine the incidence and clinical features of prednisone-induced exacerbation. In addition, we aimed to comprehensively analyze the

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clinical predictors of prednisone-induced exacerbation, especially during the initial course of therapy.

2. Patients and methods

2.1. Subjects

This study was conducted using consecutive MG patients who visited Samsung Medical Center and Seoul Medical Center in Seoul, Korea, between March 1996 and June 2003. Patients were enrolled who were aged above 20 years, had grade II MG according to the Osserman classification,[8] were being administered prednisone for the first time, and were hospitalized, so they could undergo serial neurologic examinations. We excluded patients with definite factors that would aggravate the clinical symptoms of MG, such as infection or self-discontinuation of medication. Because it is difficult to determine whether a worsening of MG symptoms is caused by the effect of prednisone or is a reflection of the natural course of the disease, we also excluded patients with severe pre-treatment fluctuation of MG symptoms, MG crisis or impending crisis prior to prednisone administration. Furthermore, we excluded patients who had recently undergone non-pharmacological therapeutic interventions that might influence the natural course of MG, for example thymectomy or plasma exchange (within 3 months prior to prednisone use).

2.2. Criteria and measurement of clinical exacerbation

In general, the clinical symptoms of MG fluctuate over time. Furthermore, clinicians usually start prednisone treatment as an add-on therapy for anti-cholinesterase-resistant MG with a clinically deteriorative course. Therefore, the extent of exacerbation caused only by prednisone is difficult to ascertain, and the influence of other factors must be minimized in order for it to be determined. For this purpose, we assessed the clinical status of patients using the Myasthenia Severity Scale (MSS)[9] (Table 1). 'Prednisone-induced exacerbation' and 'prednisone-induced improvement' were defined, respectively, as a decrease or increase in MSS score by three or more points during the initial 4 weeks of prednisone use, in patients without previous significant fluctuation of MSS score (a change of less than two points) (Fig. 1). We also assessed patients by using the Myasthenia Functional Scale (MFS)[9] to quantify neurological disability due to MG (Table 2).

2.3. Laboratory findings

We analyzed the decremental ratios of repetitive nerve stimulation tests, which were performed less than 1 month before and less than 1 month after the prednisone-induced exacerbation. We also analyzed acetylcholine receptor antibody levels during the same period.

Table 1
Myasthenia severity scale (MSS)[9]

Dyspnea
1 = Intubated
2 = Dyspnea at rest
3 = Dyspnea on exertion
4 = None

Cough
1 = Intubated
2 = Weak
3 = Normal

Ocular
1 = Weakness at rest
2 = Weakness on fatigue
3 = None

Bulbar
1 = Weakness at rest
2 = Weakness on fatigue
3 = None

Extremities
1 = Worst affected muscle 3/5 or less
2 = Worst affected muscle 4/5 motor strength or weakness on fatigue
3 = No detectable weakness

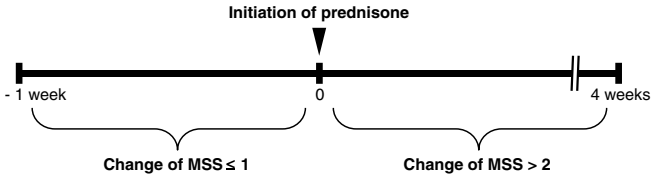

Fig. 1. Criteria of prednisone-induced exacerbation or improvement. This is defined as a condition in which significant change of MSS score (>2 points) occurs during 4 weeks of treatment with previous minimal fluctuation of MSS score (<2 points within 1 week prior to initiation of prednisone).

Table 2
Myasthenia functional scale (MFS)[9]

1 = Complete remission
2 = Minor symptoms allowing normal activity, except for exertional activity
3 = Moderate symptoms allowing occupational or partial daily activity
4 = Major disability requiring discontinuation of occupational activity or major reduction of daily activity
5 = Major disability requiring continuous help by others or mechanical ventilation

2.4. Statistical analysis

We divided the MG patients into two groups on the basis of whether or not they experienced prednisone-induced exacerbation (on the basis of the aforementioned criteria), and compared the two groups with respect to clinical, laboratory, and electrophysiological findings. Results are presented as mean ± standard deviation. We used the χ^2 test to assess differences between groups for the categorical variables, and the Mann–Whitney *U*-test for continuous variables. To identify the independent predicting factors, we performed univariate and multivariate logistic regression analysis. The

level of significance was $p < 0.05$. SPSS 10.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for the analysis.

3. Results

3.1. Comparison of clinical and laboratory findings

Twenty-three of 55 patients experienced prednisone-induced exacerbation as defined herein. Ten of these patients experienced such severe symptoms that they were admitted to the intensive care unit for approximately 10 days. Tracheostomy was performed for four patients, and long-term respiratory support was required. However, no deaths occurred because of exacerbations (Table 3).

The age of patients in the exacerbated group was significantly higher than that of patients in the non-exacerbated group. However, the age of MG onset was lower in the exacerbated group than in the non-exacerbated group. The exacerbated group had lower MSS scores and higher MFS scores than patients in the non-exacerbated group, which reflected the severe neurological symptoms and disabilities experienced by the exacerbated patients at the time steroid therapy was initiated. The exacerbated group also had a significantly higher titre of acetylcholine receptor antibodies. When reasons for the addition of prednisone to the treatment regimen, or target symptoms for prednisone, were divided into bulbar symptoms and non-bulbar symptoms, all patients in the exacerbated group were given prednisone for bulbar symptom control, compared with 60% of the non-exacerbated group. The remaining 40% of the non-exacerbated group were administered prednisone to ameliorate non-bulbar symptoms, such as weakness of the limbs or ocular symptoms.

Patients who did not respond to prednisone treatment within the first 4 weeks represented only 20% of those in the exacerbated group, but one-half of patients in the non-exacerbated group. Thus, the probability of improvement was higher in the exacerbated group than in the non-exacerbated group. Other factors, including sex, duration of MG, dosage of anti-cholinesterase (pyridostigmine) used before prednisone addition, decremental ratio of a repetitive nerve stimulation test, presence of thymoma or history of thymectomy, and dose of prednisone per kilogram body weight,

Table 3
Summary of features of myasthenia gravis patients who experienced steroid-induced exacerbation

Patients	Number (%)
Exacerbated patients	23 (42)
Patients in ICU	10 (18)
Intubated patients	10 (18)
Tracheostomized patients	4 (7)
Deaths	0 (0)
Mean duration of ICU stay (days)	11.8 ± 10.2
Mean duration of hospitalization (days)	39.8 ± 15.4

ICU, intensive care unit.

Table 4
Comparison between the steroid exacerbated and non-exacerbated myasthenia gravis groups

	Non-exacerbated ($n = 32$)	Exacerbated ($n = 23$)	p-Value
Demographic features			
Age (years)	41.1 ± 15.4	52.3 ± 13.4	0.007*
Male/female ratio	12/20	8/15	>0.99
Age at onset (years)	39.8 ± 15.4	48.5 ± 14.0	0.45
Duration of symptoms (months)	29.9 ± 36.4	40.7 ± 45.8	0.28
Previous clinical status of MG			
Previous dose of PST (mg)	215.6 ± 115.1	259.8 ± 131.9	0.32
MSS score	12.5 ± 1.6	9.4 ± 2.0	<0.001*
Functional MG scale score	3.4 ± 0.6	4.4 ± 0.6	<0.001*
Thymomatous MG (n)	14	8	0.46
Thymectomized MG (n)	17	13	0.58
Laboratory findings			
AChR-Ab level	4.5 ± 3.6	7.9 ± 5.6	0.03**
Decremental ratio of RNS (%)			
Orbicularis oculi	15.6 ± 10.8	19.2 ± 18.6	0.96
Trapezius	11.0 ± 11.1	24.9 ± 19.4	0.15
Adductor digiti minimi	3.0 ± 8.5	9.8 ± 11.1	0.35
Outcome after use of Pd			
Reason for Pd use, bulbar symptoms (n)	18	23	<0.001*
Total Pd dose (mg)	62.3 ± 14.5	66.7 ± 11.6	0.43
Dose per body weight (mg/kg)	1.1 ± 0.4	1.3 ± 0.3	0.23
Initiation of exacerbation after Pd (days)	–	2.3 ± 1.4	–
Initiation of improvement after Pd (days)	8.1 ± 4.9	11.8 ± 7.5	0.15
Non-responders (within 1 month) (n)	16	5	0.03**

PST, pyridostigmine; AChR-Ab, acetylcholine receptor antibody; RNS, repetitive nerve stimulation; Pd, prednisone; MG, myasthenia gravis; MSS, myasthenia gravis severity scale.
* $p < 0.01$.
** $p < 0.05$.

were not significantly different between the exacerbated group and the non-exacerbated group (Table 4).

3.2. Analysis of predictors

Because of the numerous possible confounding factors, multivariate logistic regression analysis was performed as to the presence or otherwise of exacerbation. We conducted the analysis using variables that had been proven to be significant factors by univariate analysis, including age, age at MG symptom onset, MSS score, titre of acetylcholine receptor antibody, and dominancy of bulbar symptoms. Although the MFS score was found to be significant by univariate analysis, it was excluded from multivariate regression analysis owing to its strong correlation with MSS score (Spearman correlation coefficient −0.796, $p < 0.001$), and consequently the possibility that it would affect the regression model because of the problem of multi-linearity. The following were identified as significant factors by multivariate logistic regression analysis: age, low MSS score, and predominant bulbar symptoms. Analysis showed that the regression model was adequate ($p < 0.001$); the R^2 value was 0.56. Hence, older age, low MSS score, and predominant bulbar symptoms accounted for about 56% of the causal relationship for the exacerbation. Although both the age of MG onset and titre of acetylcholine receptor antibody levels were found to be significant in univariate analysis, they were not significant in multivariate analysis (Table 5).

Daily doses of prednisone were between 0.6 and 1.8 mg/kg in patients enrolled in this study. We analyzed the correlation between the daily dose of prednisone per kilogram and the interval before clinical improvement for the patients who experienced clinical improvement, but we found no significant correlation between the two (Spearman's correlation, $p > 0.05$). Daily dose of prednisone per kilogram body weight was neither a significant predictor of exacerbation nor related to early improvement.

Table 5
Univariate and multivariate logistic regression analysis for predictors of steriod-induced exacerbation of myasthenia gravis

	p-value (univariate)	*p*-Value (multivariate)
Age	0.008*	0.01*
Sex	0.83	
Age at onset	0.04†	0.07
Duration of symptoms	0.34	
Previous dosage of PST	0.23	
MSS score	<0.001*	<0.001*
Functional MG scale score	<0.001*	
Presence of thymoma	0.23	
Thymectomy	0.80	
AchR-Ab level	0.01**	0.05
Predominancy of bulbar symptoms	<0.001*	0.01**
Total Pd dosage	0.24	
Dose per weight	0.23	

PST, pyridostigmine; AchR-Ab, acetylcholine receptor antibody; Pd, prednisone; MG, myasthenia gravis; MSS, myasthenia gravis severity scale.
* $p < 0.01$.
** $p < 0.05$.

4. Discussion

Currently, steroids are the mainstay of immunotherapy for MG. However, a well-designed, randomized, controlled trial proving the effectiveness of steroids for the treatment of MG has not been performed.[10] The reported frequency of steroid-induced exacerbation varies between 25% and 75%;[7,11,12] but the definition of exacerbation in these studies was inconsistent, therefore comparisons between them are difficult. Recent hypotheses for the mechanisms by which worsening occurs are: the action of released antibodies from degraded lymphocytes, increased activity of cholinesterase in neuromuscular junctions, and an overall increase in immune reactions.[13–15] However, the main mechanism is not clearly understood, despite many hypotheses. There is also ongoing debate about the optimal treatment regimen for achieving maximal efficacy and minimal side effects. Some have found that a stepwise dose elevation regimen is superior to an initial large dose regimen in preventing initial worsening;[12,16,17] however, others have noted that regimens with an initial large dose produce a rapid improvement in MG symptoms.[18–20] Because of these factors, there is a poor understanding steroid use in MG, including the incidence of side effects, the mechanisms of side effects and the optimal regimen for minimizing them. As a result, in the clinical field, judgement about steroid use in MG is largely empirical rather than evidence-based. Clinicians require information about the efficacy of steroids in MG, the likelihood of initial exacerbation and severity of exacerbation. It is also important to know what the pure effects of prednisone are and what the optimal regimen for steroid use for minimizing initial exacerbation could be.

The immunosuppressive agent we most commonly use for MG is prednisone, and we have used a high-dose regimen (40–80 mg). To prevent the exacerbation of symptoms, we usually recommend that the patient be hospitalized during prednisone treatment when the patient is older, has severe muscle weakness, or recent aggravation of bulbar symptoms. Exacerbation of MG symptoms can manifest in various ways, from a mild weakness that does not require support, through to severe exacerbation that requires respiratory support in an intensive care unit. To maximize cost-effectiveness, it is important to know which patients must be hospitalized for serious exacerbation. To determine this, we must understand the predictors of exacerbation, but there have been few reports concerning this issue.

Namba et al.[13] suggested that the more severe the MG symptoms, the more severe the prednisone-induced exacerbation may be. Chung and Myung[5] suggested that exacerbation would be more severe in patients with infiltrative thymoma. However, Seybold and Drachman found that neither epidemiological nor clinical factors were significant predictors.[12] Some authors have even claimed that the

so-called exacerbation is only a fluctuation of symptoms rather than exacerbation caused by prednisone.[21,22] We believe that the main causes of the inconsistent previous results concerning incidence and predictors of exacerbation are as follows. First, there is the problem of defining steroid-induced exacerbation. The clinical symptoms of MG tend to fluctuate. When discussing the clinical worsening of MG symptoms, clinicians must determine whether the fluctuation is a true exacerbation related to steroid use or only a transient fluctuation of symptoms unrelated to steroid use. In the present study, we tried to define the steroid-induced 'paradoxical' exacerbation of symptoms in MG, representing the pure effects of steroids. Undoubtedly, there will be some who will argue that our measurements do not represent the effects of steroids only. However, to pinpoint the effects of steroids only, we measured the MSS while steroids were administered. Although this method is obviously not ideal, the present trial may be the first to use a clinical definition of steroid-induced 'paradoxical' exacerbation in MG. Because there are no objective laboratory tools to measure the severity of MG symptoms, our clinical definition is an improvement on the subjective and obscure definitions of worsening used in previous reports. The second problem relates to factors influencing the symptoms of MG. Previous studies did not consider confounding factors such as combined MG medication (except for prednisone), the presence of thymoma, or recent plasma exchange or thymectomy. Our study included only patients who were being treated with prednisone for the first time and who had no history of being treated with other immunosuppressive agents. We analyzed the dosage of pyridostigmine at the time of prednisone addition, and we excluded patients who could have been influenced by recent interventions. These factors were not identified as significant predictors. Neither were any of the following predictors: presence of thymoma, thymectomy, or titre of acetylcholine receptor antibody.

Developed on the basis of empirical data, the large-dose prednisone regimen used in our clinic is a single dose of 60–80 mg per day. In the present study, we calculated the dosage of prednisone per kilogram body weight, and analyzed whether the dosage was related to either the probability of worsening or the rapidity of improvement. We found that neither the frequency of worsening nor the rapidity of improvement was related to the dosage of steroid used. Therefore, we concluded that if a large-dose regimen of 40–80 mg administered in a single daily dose is used to treat an adult, the dose of prednisone used does not affect either efficacy or side effects in patients with anti-cholinesterase-resistant MG.

Our study identified older age, predominant bulbar symptoms, and severe neurologic status as independent clinical predictors of steroid-induced exacerbation in MG. Therefore, we believe that close monitoring of MG symptoms during hospitalization is necessary for patients with these conditions, especially during the initial course of prednisone administration. In fact, many experienced clinicians may already consider these factors when making treatment decisions, so our study could be criticized on the basis that we identified only previously well-accepted empirical findings. However, we believe that our study can contribute by providing a small amount of clear data to guide an evidence-based approach to steroid-induced exacerbation of MG and strategies for minimizing it.

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