Journal of the Neurological Sciences 396 (2019) 8–11

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Predictive score for oral corticosteroid-induced initial worsening of seropositive generalized myasthenia gravis

Tetsuya Kanai[a], Akiyuki Uzawa[a,*], Naoki Kawaguchi[a,b], Fumiko Oda[a], Yukiko Ozawa[a], Keiichi Himuro[a,c], Satoshi Kuwabara[a]

[a] Department of Neurology, Graduate School of Medicine, Chiba University, Japan
[b] Department of Neurology, Neurology Chiba Clinic, Japan
[c] Department of Neurology, JR Tokyo General Hospital, Japan

ARTICLE INFO

Keywords:
Myasthenia gravis
Predictive score
Initial worsening
Steroid

ABSTRACT

Background: Initial worsening of symptoms after the start of corticosteroid administration is a major concern in the treatment of myasthenia gravis (MG). However, the risk factors or specific patient backgrounds related to this issue have not been fully understood. We aimed to determine the risk factors and developed a scoring system for predicting initial worsening in generalized MG.

Methods: We enrolled 62 generalized MG patients with anti-acetylcholine receptor antibody. Initial worsening was defined as an increment of three points in the Quantitative MG score within 2 weeks after the start of steroid treatment. A multivariate logistic regression model was used to determine the risk factors, and predictive scores were assigned. Bootstrap resampling was applied to evaluate the risk score model's internal validity.

Results: Steroid-induced initial worsening occurred in 26% of MG patients and was correlated with thymoma-associated or early-onset MG ($p = 0.018$), initial prednisolone doses ≥ 40 mg/day ($p = 0.029$), and upper limb weakness ($p = 0.039$). Stepwise multivariate logistic regression identified these three clinical factors for predicting initial worsening in MG. A predictive score of 0–3 points had a bootstrapping area under the curve of 0.770 (0.625–0.878).

Conclusions: Our scoring system based on three clinical characteristics can predict the likelihood of steroid-induced initial worsening in MG.

1. Introduction

Myasthenia gravis (MG) is an autoimmune-mediated disease; most patients with MG have autoantibodies against the acetylcholine receptor (AChR), and some patients have autoantibodies against the muscle-specific tyrosine kinase (MuSK) [1]. Corticosteroid administration is currently the primary choice for generalized MG treatment [2]; however, the initiation of corticosteroid treatment can lead to the transient worsening of MG symptoms in some patients [3–6]. It has been reported that the incidence of initial worsening ranged from 25% to 70% [3,4]. A gradual increase in the prednisolone dose can attenuate the severe aggravation requiring medical interventions, such as intubation, ventilation, and tubal feeding but still induces mild exacerbation [5]. Factors that provoke steroid-induced exacerbation and methods that prevent steroid-induced deterioration are major concerns for clinicians. One report revealed some risk factors such as older age, bulbar dominance, and severe myasthenic symptoms associated with initial worsening in MG [7]. Other reports have demonstrated that thymoma is a meaningful factor associated with the risk of initial worsening [6,8]. A major problem of these studies was that no precise definition of initial worsening was applied. In this study, we aimed to develop a clinical prediction score for initial worsening, based on pretreatment data obtained from patients with MG.

2. Material and methods

2.1. Study design and subjects

A total of 67 generalized MG patients with anti-AChR antibody who were admitted at the Chiba University Hospital from January 2008 to May 2017 were enrolled in this study to develop a clinical scoring system for initial worsening. Clinical and laboratory data from medical records were retrospectively analyzed. MG was diagnosed on the basis of the characteristic clinical features of MG. In addition, edrophonium

* Corresponding author at: Department of Neurology, Graduate School of Medicine, Chiba University, 1-8-1, Inohana, Chuo-ku, Chiba 260-8670, Japan.
E-mail address: auzawa@chiba-u.jp (A. Uzawa).

https://doi.org/10.1016/j.jns.2018.10.018
Received 10 March 2018; Received in revised form 3 October 2018; Accepted 18 October 2018
Available online 19 October 2018
0022-510X/

test/electrophysiological test (repetitive nerve stimulation test and/or single-fiber electromyography) positivity was required for the diagnosis of MG. We included generalized MG patients who received prednisolone for the first time in the hospital. Patients who took prednisolone before admission (n = 2), those who were intubated at admission (n = 1), and those whose clinical data were insufficient (n = 2) were excluded from the study. Finally, 62 patients were analyzed in this study. The ethics committee of the Chiba University School of Medicine approved the study, and informed consent was obtained from all study subjects.

2.2. Evaluation parameters

Our aim was to identify the risk factors for initial worsening in MG using clinical data extracted before prednisolone administration; therefore, only the clinical data collected before prednisolone administration were reviewed: gender, age at therapy and disease onset, duration between disease onset and taking prednisolone, MG subgroups, Myasthenia Gravis Foundation of America (MGFA) classification [9], Quantitative MG (QMG) Score, anti-AChR antibody titer, white blood cell count, and serum potassium concentration. Treatment factors such as initial prednisolone doses and concurrent treatments (immunosuppressants, intravenous immunoglobulin, and/or plasmapheresis) received within 1 month before the first prednisolone administration were also reviewed. Prednisone initial dose and dose-changing manner were depended on physician's decision. We used tacrolimus or cyclosporine as immunosupressants before or concurrent with initial prednisolone. Intravenous immunoglobulin and plasmapheresis were conducted before prednisolone initiation. We assessed the myasthenic symptoms using QMG score data: presence of ocular symptoms, facial palsy, bulbar palsy, dyspnea, neck weakness, upper limb weakness (grip strength was not included), and lower limb weakness are regarded as positive if the score had points. Patients with MG were classified into three subgroups: early-onset MG (EOMG), with an age at onset of < 50 years without thymoma, late-onset MG (LOMG), with an age at onset of ≥50 years without thymoma, and thymoma-associated MG (TAMG). White blood cell counts and serum potassium concentrations were also determined within 1 week after prednisolone administration. In this study, initial worsening was defined as an increment of three points in the QMG score within 2 weeks after the start of steroid treatment.

2.3. Statistical analysis

To identify the baseline and clinical variables associated with initial worsening, all parameters were evaluated using univariate logistic regression analysis for numerous outcomes and Fisher's exact test for categorical outcomes. We included all variables that existed before treatment but excluded a variable if two independent variables had a correlation of 0.6 by the Spearman rank test and performed multivariate analysis using a logistic regression model with a stepwise selection procedure. The stepwise procedure was set using a threshold of 0.05 for both inclusion and exclusion. Additionally, the Akaike information criterion was applied to determine the best model among those tested [10]. To construct a simple scoring system for clinical use, we assigned a referent risk as the nearest integer points using a regression coefficient with a base risk of 0 points. Higher total points indicated a greater risk of initial worsening. Bootstrap resampling was used to evaluate the risk score model's internal validity, which allowed for the computation of an unbiased estimate of predictive accuracy by determining the area under the receiver operating characteristic (ROC) curve (AUC). The risk score model's performance was evaluated based on the AUC obtained with the bootstrap technique using 2000 bootstrap replicate values.

All comparisons were planned and the tests were two-sided. A p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using JMP Pro 12.1.0 (SAS Institute Inc., SAS Campus Drive, Cary, NC, USA), STATA ver. 15 (College Station, Tex, USA).

3. Results

3.1. Patient profiles

The clinical characteristics of the 62 patients with MG are summarized in Table 1. The mean ± standard deviation (SD) age at onset was 58.4 (± 16.9) years and the median (interquartile range; IQR) disease duration time was 4.1 (2.5–12.4) months. Sixteen (26%) MG patients experienced steroid-induced initial worsening. The mean (± SD) period of initial worsening was 6 (± 3.1) days and all initial worsening occurred within 14 days. Three patients had severe aggravations: two tubal feeding and one mechanical ventilation. In the initial worsening group, the mean QMG scores (± SD) before treatment and after worsening were 14.6 (± 7.2) and 18.5 (± 7.2) points, respectively.

3.2. Predictive score for initial worsening risk

The clinical characteristics of patients with and without steroid-induced initial worsening are summarized in Table 1. Factors significantly associated with the occurrence of initial worsening were TAMG or EOMG, upper limb weakness, initial prednisolone dose, white blood cell count, and potassium concentration after prednisolone administration (Table 1). To determine the cut-off dose of initial prednisolone, we conducted a univariate logistic regression analysis and calculated the ROC curve. The results revealed that initial worsening was associated with the prednisolone dose (p = 0.029; AUC = 0.673), indicating a threshold dose of 40 mg/day. The incidence of worsening were 22%, 25% and 57% for doses below 20 mg, between 20 and 40 mg and over 40 mg, respectively. Initial prednisolone dose and serum potassium concentration after therapy exhibited a negative correlation of 0.342 by the Spearman rank test (p = 0.006). We have checked the prednisolone dose and other factors, including EOMG, LOMG, TAMG, MGFA, QMG score, plasmapheresis, IVIG, MG symptom; Only plasmapheresis was weakly correlated with prednisolone dose (p = 0.009, r = 0.4172). TAMG and LOMG exhibited a positive correlation of 0.649 by the Spearman rank test; therefore, we chose either one. Stepwise multivariate logistic regression revealed three factors: TAMG or EOMG, initial prednisolone dose of ≥40 mg/day, and upper limb weakness except for grip weakness (AUC = 0.774; Table 2). These three factors were incorporated into the initial worsening score (Table 3), yielding a total score ranging from 0 to 3 points. Bootstrap resampling revealed an AUC (95% confidence interval) of 0.770 (0.625–0.878). The probability of initial worsening at each point is shown in Fig. 1. The mean (± SD) critical time interval for steroid induced worsening was similar among 3 factors (5.5 ± 2.9, 5.6 ± 2.9, and 5.4 ± 2.7 days for TAMG or EOMG, upper limb weakness, and higher prednisolone doses, respectively).

4. Discussion

To the best of our knowledge, this is the first study that used an appropriate definition of worsening to establish a clinical scoring system for predicting the risk of steroid-induced initial worsening.

Although most previous studies did not refer to definitions of initial worsening, one study defined initial worsening as a decrease in the Myasthenia Severity Scale score by three points during 4 weeks of initial prednisolone use [8]. However, this definition was not ideal in two aspects: (1) assessment (the QMG score and not the Myasthenia Severity Scale is mainly used for evaluating MG severity in clinical settings: Then we have used the 3 points worsening of QMG to eliminate daily fluctuation worsening according to previous study [11].); and (2)

Table 1
Comparison of patients' characteristics with or without initial worsening.

	Total (n = 62)	Initial worsening group (n = 16)	Non–initial worsening group (n = 46)	*P* value
Age at the time of therapy, years	59.4 ± 16.8	53.3 ± 15.5	61.5 ± 16.9	0.096
Age at onset, years	58.4 ± 16.9	52.3 ± 15.6	60.5 ± 16.8	0.097
Sex (male/female)	26/36	6/10	20/26	0.759
Disease duration, months	4.1 (2.5–12.4)	5.1 (1.7–12.8)	3.9 (3.0–12.8)	0.897
E-L-T classification				0.002
Early-onset MG, n (%)	12 (19%)	4 (25%)	8 (17%)	0.487
Late-onset MG, n (%)	33 (53%)	3 (19%)	30 (65%)	0.008
Thymoma-associated MG, n (%)	17 (27%)	9 (56%)	8 (17%)	0.018
Thymoma histopathology				0.217
Microscopic thymoma	2 (12%)	0 (0%)	2 (25%)	
AB	2 (12%)	1 (11%)	1 (13%)	
B1	2 (12%)	2 (22%)	0 (0%)	
B2	9 (53%)	5 (56%)	4 (50%)	
B3	2 (12%)	1 (11%)	1 (13%)	
MGFA, n (%)				0.329
II	49 (79%)	11 (69%)	42 (84.0%)	
III	10 (16%)	4 (25.0%)	6 (12.0%)	
IV	3 (5%)	1 (6.2%)	2 (4.0%)	
AChR titer, nmol/L (median [IQR]), n = 62	40 (11–80)	41 (22–118)	39 (11–69)	0.567
White blood cell counts before prednisolone,/mm^3 (mean ± SD)	5798 ± 1391	5518 ± 1031	5895 ± 1494	0.339
White blood cell counts after prednisolone/mm^3 (mean ± SD)	7414 ± 3201	6243 ± 1619	7821 ± 3515	0.045
Potassium concentration before prednisolone, mEq/L (mean ± SD)	4.1 ± 0.4	4.0 ± 0.2	4.1 ± 0.4	0.260
Potassium concentration after prednisolone, mEq/L (mean ± SD)	3.8 ± 0.4	3.6 ± 0.2	3.9 ± 0.4	0.045
Quantitative MG Score before treatment, points (mean ± SD)	13.2 ± 5.8	14.6 ± 7.2	12.8 ± 5.3	0.336
Ocular symptoms, n (%)	60 (97%)	16 (100%)	44 (96%)	1.000
Facial palsy, n (%)	37 (60%)	7 (44%)	30 (65%)	0.150
Bulbar palsy, n (%)	18 (29%)	5 (31%)	13 (28%)	1.000
Dyspnea, n (%)	20 (32%)	6 (38%)	14 (30%)	0.752
Neck weakness, n (%)	53 (85%)	13 (81%)	40 (87%)	0.683
Upper limb weakness, n (%)	33 (53%)	12 (75%)	21 (46%)	0.039
Lower limb weakness, n (%)	38 (61%)	10 (63%)	28 (61%)	1.000
Initial prednisolone dose, mg/day	17.6 ± 13.3	24.1 ± 17.1	15.3 ± 11.0	0.029
Immunosuppressant, n (%)	7 (11%)	0 (0.0%)	7 (15%)	0.175
Plasmapheresis, n (%)	14 (23%)	7 (44%)	7 (16%)	0.035
Intravenous immunoglobulin, n (%)	5 (8%)	1 (6%)	4 (9%)	1.000

AChR: acetylcholine receptor, IQR: interquartile range, MG: myasthenia gravis, MGFA: Myasthenia Gravis Foundation of America, SD: standard deviation.

Table 2
Estimates of the parameters of the multivariable model (AUC = 0.774).

Risk factor	Regression coefficient	Adjusted OR	95% CI	P
Intercept	0.648	–	–	0.173
TAMG or EOMG	0.703	4.1	1.0–15.9	0.042
Upper limb weakness	0.686	3.9	1.0–16.9	0.064
Initial prednisolone dose ≥ 40 mg	0.921	6.3	1.0–41.5	0.055

AUC: area under the curve, CI: confidence interval, EOMG: early-onset MG, MG; myasthenia gravis, TAMG: thymoma-associated MG.

duration (initial worsening usually lasts for up to 3 weeks [1] and not 4 weeks).

It has been thought that steroid-induced exacerbation occurs in a dose-dependent manner; prednisolone doses of 25 mg/alternate day, 0.8 mg/kg/day, and 60 mg/day led to initial worsening in 0%, 21%, and 44% of MG patients, respectively [5,12,13]. However, no reference dose of initial prednisolone that contributes to initial worsening in MG is available. We showed that the higher prednisolone doses were

Table 3
Predictive score for initial worsening.

	Category	Score
TAMG or EOMG	Yes	1
	No	0
Upper limb weakness	Yes	1
	No	0
Initial prednisolone dose	≥ 40 mg/day	1
	< 40 mg/day	0

EOMG: early-onset MG, MG: myasthenia gravis, TAMG: thymoma-associated MG.

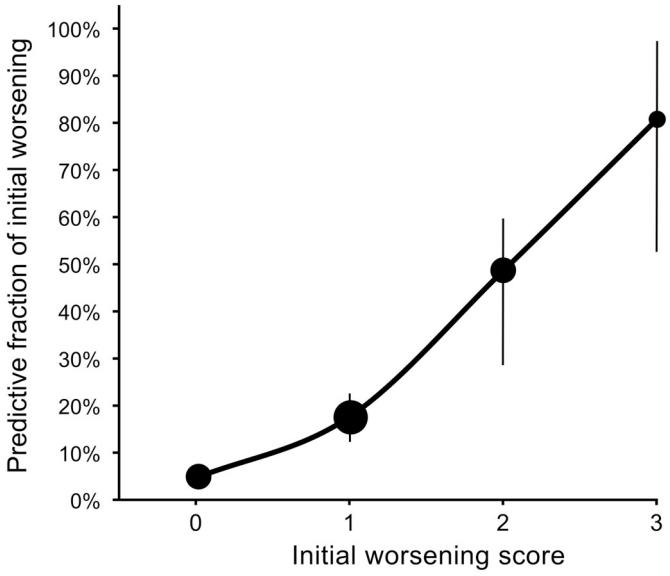

Fig. 1. Predicted risk of initial worsening. The probability of initial worsening was calculated using the predictive score. Point sizes are proportional to the number of patients with a specific score. Vertical bars indicate the 95% confidence interval.

associated with higher risk of initial worsening in MG symptoms. Hypotheses for the mechanisms of initial worsening are the action of released AChR or MuSK antibodies induced by lympholysis, increased activity of cholinesterase in neuromuscular junctions, and direct affection of neuromuscular transmission with the increment in miniature end-plate potentials (MEPPs) frequency following a decrease in MEPP amplitude by ~50% [14–16]. We checked the white blood cell count and serum potassium concentration before and after prednisolone therapy. Lower serum potassium concentrations after therapy were related to initial worsening and initial prednisolone dose ($p = 0.044$ and 0.003, respectively), indicating that high-dose prednisolone induced the reduction of serum potassium concentrations following the hyperpolarization of resting membrane potentials.

The presence of upper limb weakness was identified as a predictor of the risk of steroid-induced initial worsening in MG. The severity of MG could be a major risk factor for initial worsening according to previous studies [6,7,17]. Therefore, we assessed the association between MG symptoms (ocular symptoms, facial palsy, bulbar palsy, dyspnea, neck weakness, upper limb weakness, and lower limb weakness) and MG severity (QMG score and MGFA classification). Some MG symptoms were significantly related to the QMG score (bulbar palsy, $p < 0.001$, $r = 0.4896$; dyspnea, $p = 0.003$, $r = 0.3613$; neck weakness, $p = 0.0007$, $r = 0.4193$; upper limb weakness, $p < 0.0001$, $r = 0.6680$; and lower limb weakness, $p < 0.0001$, $r = 0.6519$), but only upper limb weakness was associated with the pre-treatment MGFA classification ($p = 0.013$, $r = 0.3158$). Among the MG symptoms, upper limb weakness could be the most sensitive indicator of steroid-induced initial worsening.

In this study, the presence of thymoma was also identified to be associated with initial worsening in MG. Two studies have suggested that steroid-induced exacerbation of MG symptom would be more severe in patients with thymoma [6,8]. Prednisolone is used as a first-line chemotherapy for thymoma [18], meaning that tumor lysis induced by prednisolone would contribute to the cytokine reaction [19] that leads to initial worsening. In addition to TAMG, EOMG was detected as a candidate of the score. Thymocytes are more abundant in EOMG thymus than LOMG thymus. Glucocorticoids are known to induce apoptosis in thymocytes [20], similarly activating cytokine reaction.

Another factor related to the risk of steroid-induced initial worsening was the age at the start of therapy [7]. We could not determine the association between age and initial worsening in our study. This discrepancy may be due to the differences in age: the mean age of our patients was 59.4 years, whereas that of patients in a previous study was 45.8 years [7].

Some limitations in this study need to be addressed. Our predictive score for steroid-induced initial worsening was based on a retrospective research, which might restrict its general applicability. Patients who did not have sufficient clinical data were excluded, which may have resulted in selection bias. Although we showed 3 factors (TAMG or EOMG, upper limb weakness, and high dose prednisolone) to predict steroid-induced initial worsening, the pathophysiology has not been clarified yet. Further analyses about the steroid-induced worsening of MG will be required.

In conclusion, our predictive score for steroid-induced initial worsening was based on three pre-therapy clinical parameters: TAMG or EOMG, initial dose of prednisolone of ≥ 40 mg/day, and presence of upper limb weakness. It showed adequate value and could be a useful indicator to predict steroid-induced initial worsening.

Funding

No funding was received for this study.

Acknowledgment

None.

References

[1] N.E. Gilhus, J.J. Verschuuren, Myasthenia gravis: subgroup classification and therapeutic strategies, Lancet Neurol. 14 (2015) 1023–1036.
[2] R. Gold, R. Hohlfeld, K.V. Toyka, Progress in the treatment of myasthenia gravis, Ther. Adv. Neurol. Disord. 1 (2008) 36–51.
[3] R.B. Jenkins, Treatment of myasthenia gravis with prednisone, Lancet 1 (1972) 765–767.
[4] N.G. Brunner, T. Namba, D. Grob, Corticosteroids in management of severe, generalized myasthenia gravis. Effectiveness and comparison with corticotropin therapy, Neurology 22 (1972) 603–610.
[5] M.E. Seybold, D.B. Drachman, Gradually increasing doses of prednisone in myasthenia gravis. Reducing the hazards of treatment, N. Engl. J. Med. 290 (1974) 81–84.
[6] J.D. Mann, T.R. Johns, J.F. Campa, Long-term administration of corticosteroids in myasthenia gravis, Neurology 26 (1976) 729–740.
[7] J.S. Bae, S.M. Go, B.J. Kim, Clinical predictors of steroid-induced exacerbation in myasthenia gravis, J. Clin. Neurosci. 13 (2006) 1006–1010.
[8] C.S. Chung, H.J. Myung, A clinical study on crisis in myasthenia gravis, J. Korean Neurol. Assoc. 2 (1984) 29–39.
[9] A. Jaretzki III, R.J. Barohn, R.M. Ernstoff, et al., Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America, Neurology 55 (2000) 16–23.
[10] H. Akaike, A new look at the statistical model identification, IEEE Trans. Autom. Control 19 (1974) 716–723.
[11] S. Muppidi, Outcome measures in Myasthenia Gravis: incorporation into clinical practice, J. Clin. Neuromuscul. Dis. 18 (2017) 135–146.
[12] A. Evoli, A.P. Batocchi, M.T. Palmisani, M. Lo Monaco, P. Tonali, Long-term results of corticosteroid therapy in patients with myasthenia gravis, Eur. Neurol. 32 (1992) 37–43.
[13] R.M. Pascuzzi, H.B. Coslett, T.R. Johns, Long-term corticosteroid treatment of myasthenia gravis: report of 116 patients, Ann. Neurol. 15 (1984) 291–298.
[14] R.W. Wilson, M.D. Ward, T.R. Johns, Corticosteroids: a direct effect at the neuromuscular junction, Neurology 24 (1974) 1091–1095.
[15] R.G. Miller, H.S. Milner-Brown, A. Mirka, Prednisone-induced worsening of neuromuscular function in myasthenia gravis, Neurology 36 (1986) 729–732.
[16] E. Arsura, N.G. Brunner, T. Namba, D. Grob, High-dose intravenous methylprednisolone in myasthenia gravis, Arch. Neurol. 42 (1985) 1149–1153.
[17] E.S. Kim, J.B. Putnam, R. Komaki, et al., Phase II study of a multidisciplinary approach with induction chemotherapy, followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable malignant thymomas: final report, Lung Cancer 44 (2004) 369–379.
[18] S.C. Howard, D.P. Jones, C.H. Pui, The tumor lysis syndrome, N. Engl. J. Med. 364 (2011) 1844–1854.
[19] T. Namba, N.G. Brunner, D. Grob, Myasthenia gravis in patients with thymoma, with particular reference to onset after thymectomy, Medicine (Baltimore) 57 (1978) 411–433.
[20] M.S. Vacchio, J.D. Ashwell, L.B. King, A positive role for thymus-derived steroids in formation of the T-cell repertoire, Ann. N. Y. Acad. Sci. 840 (1998) 317–327.