Causal background factors for depressive state in myasthenia gravis patients: a multicenter cooperative study

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Causal background factors for depressive state in myasthenia gravis patients : a multicenter cross-sectional study

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Key words: corticosteroids; depressive state; disease severity; myasthenia gravis; postintervention status

ABSTRACT

Purpose: To examine causal background factors for depressive state in patients with myasthenia gravis (MG).

Methods: We evaluated 287 consecutive cases of MG seen at 6 neurological centers. All MG patients completed the Japanese version of the Beck Depression Inventory-Second Edition (BDI-II). Disease severity was determined according to the MG Foundation of America (MGFA) quantitative MG score (QMG), MG activities of daily living scale (MG-ADL) and MG composite scale (MG composite). Clinical state following treatment was categorized according to MGFA postintervention status. Associations between detailed clinical parameters of MG and BDI-II score were then examined statistically.

Results: Mean BDI-II score for MG patients (11.0±8.1) did not differ substantially from and overlapped with that reported as the Japanese standard (8.7±6.4). The mean +2 standard deviations for the Japanese standard is 21.5, approximately equal to the cut-off level indicative of moderate or worse depression (>20 points) in the original English version. We thus defined BDI-II >21.5 as depressive state, with a frequency of 13.6% in MG patients. Multivariate logistic regression analysis revealed current dose of oral prednisolone (odds ratio (OR), 1.09; p=0.01), unchanged MGFA postintervention status (OR, 3.55; p=0.02), time since onset (OR, 0.93; p=0.03) and MG composite (OR, 1.16; p=0.046) as factors independently associated with depressive state in MG.

Conclusions: Dose of oral corticosteroids appears to represent the major cause of depressive state in MG. Unchanged status despite treatment and early disease stage are also significant background factors for depressive state, along with disease severity.

ARTICLE SUMMARY

Article focus

Background factors for depressive state in myasthenia gravis (MG) were statistically examined.

Key messages

Dose of oral corticosteroids appears to represent the major cause of depressive state in MG.

Unchanged status despite treatment and early disease stage are also significant background factors for depressive state, along with disease severity.

Achieving early improvement of disease by adequate MG therapy without long-term use of higher-dose oral corticosteroids may be important to avoiding depressive state in MG patients.

Strengths and limitations of this study

Strength: this study probably is the first systematically and statistically examined associations between detailed disease-related parameters of MG and depressive state.

Limitation: predictive modeling cannot be strictly performed on this cross-sectional sample.

Weakness: the absence of social factors as variables.

INTRODUCTION

Individuals with myasthenia gravis (MG) face difficulty in maintaining daily activities and are required to cope with a chronic condition of weakness and fatigability of variable and fluctuating severity,[1,2]. Chronic and disabling disease conditions often lead to psychiatric consequences, such as anxiety and depressive disorders,[1,2]. The constant need for medications may decrease quality of life and cause psychological stress,[1,2]. Depressive symptoms have long been suggested to be common in patients with MG and extent to which and how depressive symptoms are involved in MG has been a matter of some discussion,[1-4]. However, disease-specific psychopathological backgrounds remain undefined and results from psychological testing have been inconsistent,[1-3]. The frequency of depressive symptoms in MG patients has also been inconsistently reported using different measures,[1-3]. Although an intricate relationship to MG appears to exist, previous studies were small-scale and did not clearly show causal backgrounds of depressive symptoms in MG,[1,2].

The present study evaluated self-reported symptoms of depression in a sample of 287 MG patients using a standardized measure, the Beck Depression Inventory-Second Edition (BDI-II),[5,6], and systematically and statistically examined associations with detailed clinical parameters of MG. The purpose of this study was to clarify causal background factors for depressive state in MG patients.

PATIENTS AND METHODS

Patients (Table 1)

This cross-sectional study was conducted at 6 neurological centers located in Eastern Japan (3 in Tohoku district and 3 in Tokyo area, East Japan MG study group). We evaluated 287 consecutive non-demented patients with MG seen at Sendai Medical Center, Hanamaki

General Hospital, Tohoku University Hospital, Keio University Hospital, Tokyo Medical University Hospital, or Tokyo Women's Medical University Hospital from May until August 2010. To avoid a potential bias, we enrolled consecutive patients during short duration (three months). Patients with any missing clinical data were excluded. All patients provided written informed consent and were subjected to analysis. Clinical background data for the 287 MG patients are shown in Table 1.

The diagnosis of MG was based on clinical findings (fluctuating symptoms with easy fatigability and recovery after rest) with reductions in symptoms after intravenous administration of anticholinesterase, decremental muscle response to a train of low-frequency repetitive nerve stimuli, or the presence of antibodies against the acetylcholine receptor of skeletal muscle (AChR-Ab) or against muscle-specific tyrosine kinase (MuSK-Ab). Single-fiber EMG was not systematically examined. AChR-Ab-negative cases comprised 55 of 287 patients. Two of the 55 AChR-Ab-negative patients were MuSK-Ab-positive.

Clinical parameters

All patients completed the BDI-II, a 21-item, self-administered questionnaire designed to detect symptoms of depression and assess the severity of depression,[5,6]. BDI-II has been shown to represent a reliable and valid measure of depression,[5,6]. According to standardized scoring guidelines in the original English version, scores were categorized as indicative of moderate (20-28 points), or severe depression (≥29 points),[5,6,7]. The Japanese version of the BDI-II has also been validated and the mean score of the Japanese standard population reported as 8.7±6.4,[8], somewhat lower than that of the original English version.

Clinical factors shown in Table 1 were evaluated for each patient and entered into analysis. Clinical severity at study entry was determined by patients and participating

neurologists according to the MG Foundation of America (MGFA) quantitative MG score (QMG),[9], MG activities of daily living scale (MG-ADL),[10] and MG composite scale (MG composite),[11]. Clinical state at study entry following treatment was categorized according to MGFA postintervention status,[9]. The worst condition for each patient was classified according to the MGFA classification,[9]. Prednisone and prednisolone (PSL) are the standard agents for oral corticosteroid therapy in MG and PSL is generally used in Japan. Dose of oral PSL was evaluated for both the current and maximum dosage.

Serum AChR-Ab titers were estimated by radioimmunoassay using ^{125}I-α-bungarotoxin, with levels ≥0.5 nM regarded as positive. MG-specific autoantibodies to voltage-gated potassium channel (Kv1.4-Ab) were detected by immunoprecipitation assay using ^{35}S-labeled cellular extracts as the antigen source, as described elsewhere,[12]. Autoantibodies to titin (titin-Ab) was detected using a commercially available enzyme-linked immunosorbent assay (DLD Diagnostika, Hamburg, Germany). MuSK-Ab was measured using a commercially available radioimmunoprecipitation assay (RSR, Cardiff, UK).

All clinical information and blood samples were obtained after providing informed consent, and the study protocols were approved by the ethics committees of each institute. None of the authors have any conflicts of interest.

Statistics

Correlations between clinical factors and BDI-II score were evaluated using Pearson's correlation for continuous variables or Spearman's rank correlation for categorical variables converted to numerical variables. Factors found to have a value of $p<0.05$ in univariate analysis were entered into multivariate linear regression analysis.

Clinical factors associated with depressive state indicated by BDI-II >21.5 were

examined by logistic regression analysis. Clinical factors found to have a value of $p<0.05$ in univariate analysis were entered into multivariate logistic regression analysis to determine background factors independently associated with depressive state.

Values of $p<0.05$ were considered statistically significant. All continuous data are expressed as mean ± standard deviation (SD). Statistical analyses were performed using UNISTAT version 5.6 statistical software (Unistat, London, UK).

RESULTS

Correlations of clinical factors to BDI-II score (Table 1)

Positive correlations to BDI-II score were found for female sex, total QMG, ocular QMG, bulbar QMG, MG composite, MG-ADL, MGFA classification at the worst condition, current dose of PSL, and Improved (I) and Unchanged (U) MGFA postintervention status (Table 1). Negative correlations were seen for AChR-Ab-positivity, and Complete Stable Remission (CSR) and Minimal Manifestations (MM) MGFA postintervention status (Table 1). These clinical factors were entered into multivariate linear regression analysis, which revealed severity (MG composite, $p=0.008$; MG-ADL, $p=0.003$) and current dose of PSL ($p=0.0002$) as factors with independent positive effects on BDI-II total score. However, as mean BDI-II score for the 287 MG patients was 11.0±8.1 and did not differ substantially from and overlapped with that reported as the Japanese standard (8.7±6.4),[8], determining causal background factors for depressive state in MG using a linear regression model was potentially inappropriate. We therefore conducted further examinations using another regression model.

Table 1. Backgrounds of patients and correlations of clinical factors with BDI-II score (Pearson's correlation or Spearman's rank correlation#)

Clinical factors	*Patient Backgrounds (287 in total)*	Correlation (95% CI)	*P*
Age (years)	*57.5 ± 17.1*	-0.05 (-0.16 – 0.07)	0.200
Female#	*n=193*	0.19 (0.07 – 0.30)	0.001*
Time since onset (years)	*8.9 ± 8.3*	-0.08 (-0.19 – 0.04)	0.10
Age at onset (years)	*48.0 ± 18.6*	-0.01 (-0.13 – 0.10)	0.41
Thymectomy#	*n=141*	0.02 (-0.10 – 0.13)	0.39
Thymoma#	*n=63*	0.06 (-0.05 – 0.18)	0.15
QMG	*7.0 ± 5.1*	0.33 (0.22 – 0.43)	<0.0001*
Ocular QMG	*1.7 ± 1.8*	0.29 (0.17 – 0.39)	<0.0001*
Bulbar QMG	*0.3 ± 0.8*	0.14 (0.02 – 0.25)	0.01*
MG composite	*5.8 ± 5.7*	0.40 (0.30 – 0.50)	<0.0001*
MG ADL	*3.4 ± 3.1*	0.39 (0.29 – 0.49)	<0.0001*
MGFA classification (Worst)#	I/II/III/IV/V: *68/125/60/12/22*	0.17 (0.05 – 0.28)	0.002*
Current dose of PSL (mg/day)	*4.6 ± 5.9*	0.33 (0.22 – 0.43)	<0.0001*
Maximum dose of PSL (mg/day)	*20.5 ± 20.7*	0.02 (-0.09 – 0.14)	0.34
Calcineurin inhibitors#	*n=115*	0.07 (-0.04 – 0.19)	0.10
Crisis#	*n=22*	0.02 (-0.10 – 0.14)	0.38
AChR-Ab positivity#	*n=232*	-0.14 (-0.25 – -0.02)	0.01*
Kv 1.4-Ab positivity#	*n=37*	0.05 (-0.08 – 0.18)	0.22
Titin-Ab positivity#	*n=53*	0.09 (-0.07 – 0.26)	0.10
MuSK-Ab positivity#	*n=2 (of 55 AChR Ab-negative patients)*	Not determined	Not determined
CSR#	*n=21*	-0.10 (-0.22 – 0.01)	0.04*
PR#	*n=22*	-0.09 (-0.20 – 0.03)	0.08
MM#	*n=95*	-0.17 (-0.28 – -0.06)	0.002*
I#	*n=91*	0.12 (0.01 – 0.23)	0.02*
U#	*n=54*	0.13 (0.02 – 0.24)	0.01*
W#	*n=4*	0.03 (-0.08 – 0.15)	0.28

*Variables entered into multivariate regression analysis (see the Results section in the text)

AChR-Ab, antibodies against acetylcholine receptor; CI, confidence interval; CSR, complete stable remission; I, improved; Kv1.4, voltage-gated potassium channel 1.4; MG-ADL, MG activities of daily living scale; MG composite, MG composite scale; MGFA, Myasthenia Gravis Foundation of America; MM, minimal manifestations; MuSK, muscle-specific tyrosine kinase; PR, pharmacologic remission; PSL, prednisolone; QMG, MGFA quantitative MG score; U, unchanged; W, worse.

Factors associated with depressive state (Table 2)

Mean +2 SD for the Japanese standard BDI-II score is 21.5,[8], approximately equal to the cut-off level indicative of moderate or worse depression (BDI-II >20) in the original English version,[5,6,7]. We thus defined BDI-II >21.5 as indicating depressive state, with a frequency of 13.6% (39 of 287) among MG patients in this study. In the present subjects, as no patients showed BDI-II = 21, the total of 39 patients with depressive state using our definition (BDI-II >21.5) was identical to the result we would have achieved if a cut-off of BDI-II >20 had been used.

Clinical factors associated with depressive state were examined by logistic regression analysis. Factors displaying a value of $p<0.05$ in univariate logistic regression analysis were time since onset, QMG, ocular QMG, MG composite, MG-ADL, current dose of PSL, use of calcineurin inhibitors, and U and Worse (W) MGFA postintervention status (Table 2). These factors were entered into multivariate logistic regression analysis for determination of independent causal background factors for depressive state. Multivariate logistic regression analysis revealed current dose of PSL (odds ratio (OR), 1.09; 95% confidence interval (CI), 1.02-1.17; p=0.01), U of MGFA postintervention status (OR, 3.55; 95%CI, 1.18-10.71; p=0.02), time since onset (OR, 0.93; 95%CI, 0.87-0.99; p=0.03), and MG composite (OR,

1.16; 95%CI, 1.00-1.34; p=0.046) as independent causal background factors for depressive state in MG.

Table 2. Clinical factors associated with depressive state (univariate logistic regression)

Clinical factors	Odds ratio (95% CI)	*P*
Age (years)	0.98 (0.96 – 1.00)	0.060
Female	1.41 (0.63 – 3.14)	0.41
Time since onset (years)	0.94 (0.89 – 1.00)	0.041*
Age at onset (years)	0.99 (0.97 – 1.01)	0.51
Thymectomy	0.39 (0.18 – 1.24)	0.27
Thymoma	0.91 (0.38 – 2.20)	0.84
QMG	1.12 (1.05 – 1.19)	0.0007*
Ocular QMG	1.26 (1.05 – 1.52)	<0.012*
Bulbar QMG	1.36 (0.94 – 1.98)	0.10
MG composite	1.14 (1.08 – 1.20)	<0.0001*
MG ADL	1.21 (1.09 – 1.35)	0.0003*
MGFA classification (worst)	1.19 (0.88 – 1.62)	0.26
Current dose of PSL (mg/day)	1.09 (1.04 – 1.15)	0.0006*
Maximum dose of PSL (mg/day)	1.00 (0.98 – 1.02)	0.97
Calcineurin inhibitors	2.07 (1.01 – 4.27)	0.048*
Crisis	0.93 (0.26 – 3.29)	0.91
AChR-Ab positivity	1.00 (1.00 – 1.01)	0.28
Kv 1.4-Ab positivity	1.92 (0.70 – 5.26)	0.20
Titin-Ab positivity	1.71 (0.93 – 3.14)	0.10
CSR (no case with BDI-II >21.5)	Not determined	Not determined
PR	0.30 (0.04 – 2.28)	0.24
MM	0.54 (0.24 – 1.24)	0.15
I	1.24 (0.59 – 2.60)	0.57
U	3.14 (1.46 – 6.77)	0.004*
W	5.93 (1.27 – 27.73)	0.023*

*Variables entered into multivariate logistic regression analysis (see the Results section in the

text)

AChR-Ab, antibodies against acetylcholine receptor; CI, confidence interval; CSR, complete stable remission; I, improved; Kv1.4, voltage-gated potassium channel 1.4; MG-ADL, MG activities of daily living scale; MG composite, MG composite scale; MGFA, Myasthenia Gravis Foundation of America; MM, minimal manifestations; MuSK, muscle-specific tyrosine kinase; PR, pharmacologic remission; PSL, prednisolone; QMG, MGFA quantitative MG score; U, unchanged; W, worse.

DISCUSSION

The present study examined associations between detailed parameters of MG and self-reported depressive symptoms and revealed current dose of oral PSL as the most significant causal background for depressive state in MG. In fact, long-term use of corticosteroids has been suggested to affect the brain and result in the development of depressive conditions,[13-15]. Complications of long-term corticosteroid use emerge at around 10 mg/day of prednisone or PSL,[13-15]. Consistently, mean dose of oral PSL in MG patients with depressive state was 8.1 mg/day, significantly higher than that in patients without depressive state (3.9 mg/day; $p<0.05$ using Mann-Whitney U-test). Although oral corticosteroids represent the first-line and most common agents for immunosuppressive treatment of MG,[16], the present results indicate a possible need for attention to dose and associated depressive side effects. The constant need for medication itself might also cause psychological stress, but use of calcineurin inhibitors was not associated with depressive state.

BDI-II score for MG patients did not differ substantially from and overlapped with that of the Japanese standard. The frequency of individuals with depressive state (BDI-II >21.5) was 13.6% in this study, lower than that reported by Fisher et al.,[7]. They reported

that moderate or worse depression (BDI-II >20 in the original English version) was observed in 33% (15/45) of MG patients,[7]. The frequency of MG patients with depressive symptoms has been inconsistent in previous reports,[1-3]. Anxiety or depressive disorders have been reported as more frequent among patients with MG than in the general population,[4, 17]. Conversely, several authors have found no increased frequency of depression among MG patients compared to the general population,[18-20]. Regarding such discrepancies, given that the present study showed depressive symptoms to be positively correlated with both severity of MG and corticosteroid dose, frequency of depressive MG patients may alter depending on such background factors in subjects.

The present analysis revealed that unchanged status despite treatment and early disease stage are also significant background factors for depressive state, along with disease severity. These findings suggest that achieving early improvement of disease by adequate somatic therapy against MG may be important to avoid a depressive state,[3,18]. Psychiatric symptoms have also been noted to emerge temporarily in exacerbated MG patients, reversing if adequate somatic therapy is given,[3,4].

Lack of formal evaluation of psychopathological characteristics by psychiatrists may represent a limitation to the present study. MG patients have been suggested to exhibit symptoms characteristically similar to the vegetative signs of affective disorders, which may interfere with correct assessment of mood if using only self-rating depression scales,[19,20].

In conclusion, dose of oral corticosteroids appears to represent the major cause of depressive state in MG patients. Unchanged status despite treatment and early disease stage are also significant background factors for depressive state, along with disease severity. Achieving early improvement of disease by adequate MG therapy without long-term use of higher-dose oral corticosteroids may be important to avoiding depressive state in MG patients.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Pages 5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Pages 5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pages 5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pages 6-7
Bias	9	Describe any efforts to address potential sources of bias	Page 6
Study size	10	Explain how the study size was arrived at	Pages 5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pages 6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Pages 7-8
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable
		(*c*) Explain how missing data were addressed	Page 6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Not applicable
		(b) Give reasons for non-participation at each stage	Not applicable

		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Page 6; Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	Not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Not applicable
		(*b*) Report category boundaries when continuous variables were categorized	Page 10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	Pages 12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 4 (ARTICLE SUMMARY)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pages 12-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Factors associated with depressive state in myasthenia gravis patients : a multicenter cross-sectional study

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ABSTRACT

Objectives: To examine clinical factors associated with depressive state in patients with myasthenia gravis (MG).

Design: Cross-sectional study

Setting and Participants: We evaluated 287 consecutive cases of MG seen at 6 neurological centers located in Eastern Japan.

Outcome measures: All MG patients completed the Japanese version of the Beck Depression Inventory-Second Edition (BDI-II). Disease severity was determined according to the MG Foundation of America (MGFA) quantitative MG score (QMG), MG activities of daily living scale (MG-ADL) and MG composite scale (MG composite). Clinical state following treatment was categorized according to MGFA postintervention status. Associations between detailed clinical parameters of MG and BDI-II score were then examined statistically.

Results: Mean BDI-II score for MG patients (11.0±8.1) did not differ substantially from and overlapped with that reported as the Japanese standard (8.7±6.4). The mean +2 standard deviations for the Japanese standard is 21.5, approximately equal to the cut-off level indicative of moderate or worse depression (>20 points) in the original English version. We thus defined BDI-II >21.5 as depressive state, with a frequency of 13.6% in MG patients. Multivariate logistic regression analysis revealed current dose of oral prednisolone (odds ratio (OR), 1.09; 95% confidence interval (CI), 1.02-1.17; p=0.01), unchanged MGFA postintervention status (OR, 3.55; 95%CI, 1.18-10.71; p=0.02), time since onset (OR, 0.93; 95%CI, 0.87-0.99; p=0.03), and MG composite (OR, 1.16; 95%CI, 1.00-1.34; p=0.046) as factors independently associated with depressive state in MG.

Conclusions: Dose of oral corticosteroids appears to represent the major factor associated with depressive state in MG. Unchanged status despite treatment and early disease stage are

also significant background factors for depressive state, along with disease severity.

ARTICLE SUMMARY

Article focus

Background factors associated with depressive state in myasthenia gravis (MG) were statistically examined.

Key messages

Dose of oral corticosteroids appears to represent the major factor associated with depressive state in MG. Unchanged status despite treatment and early disease stage are also significant background factors for depressive state, along with disease severity.

Achieving early improvement of disease by adequate MG therapy without long-term use of higher-dose oral corticosteroids may be important to avoiding depressive state in MG patients.

Strengths and limitations of this study

Strength: this study probably is the first systematically and statistically examined associations between detailed disease-related parameters of MG and depressive state.

Limitation: predictive modeling cannot be strictly performed on this cross-sectional sample.

Weakness: the absence of social factors as variables.

INTRODUCTION

Individuals with myasthenia gravis (MG) face difficulty in maintaining daily activities and are required to cope with a chronic condition of weakness and fatigability of variable and fluctuating severity,[1,2]. Chronic and disabling disease conditions often lead to psychiatric consequences, such as anxiety and depressive disorders,[1,2]. The constant need for medications may decrease quality of life and cause psychological stress,[1,2]. Depressive symptoms have long been suggested to be common in patients with MG and extent to which and how depressive symptoms are involved in MG has been a matter of some discussion,[1-4]. However, disease-specific psychopathological backgrounds remain undefined and results from psychological testing have been inconsistent,[1-3]. The frequency of depressive symptoms in MG patients has also been inconsistently reported using different measures,[1-3]. Although an intricate relationship to MG appears to exist, previous studies were small-scale and did not clearly show causal backgrounds of depressive symptoms in MG,[1,2].

The present study evaluated self-reported symptoms of depression in a sample of 287 MG patients using a standardized measure, the Beck Depression Inventory-Second Edition (BDI-II),[5,6], and systematically and statistically examined associations with detailed clinical parameters of MG. The purpose of this study was to clarify clinical factors associated with depressive state in MG patients.

PATIENTS AND METHODS

Patients (Table 1)

This cross-sectional study was conducted at 6 neurological centers located in Eastern Japan (3 in Tohoku district and 3 in Tokyo area, East Japan MG study group). We evaluated 287 consecutive non-demented patients with MG seen at Sendai Medical Center, Hanamaki

General Hospital, Tohoku University Hospital, Keio University Hospital, Tokyo Medical University Hospital, or Tokyo Women's Medical University Hospital from May until August 2010. To avoid a potential bias, we enrolled consecutive patients during short duration (three months). Patients with any missing clinical data were excluded. All patients provided written informed consent and were subjected to analysis. Clinical background data for the 287 MG patients are shown in Table 1.

The diagnosis of MG was based on clinical findings (fluctuating symptoms with easy fatigability and recovery after rest) with reductions in symptoms after intravenous administration of anticholinesterase, decremental muscle response to a train of low-frequency repetitive nerve stimuli, or the presence of antibodies against the acetylcholine receptor of skeletal muscle (AChR-Ab) or against muscle-specific tyrosine kinase (MuSK-Ab). Single-fiber EMG was not systematically examined. AChR-Ab-negative cases comprised 55 of 287 patients. Two of the 55 AChR-Ab-negative patients were MuSK-Ab-positive.

Clinical parameters

All patients completed the BDI-II, a 21-item, self-administered questionnaire designed to detect symptoms of depression and assess the severity of depression,[5,6]. BDI-II has been shown to represent a reliable and valid measure of depression,[5,6]. According to standardized scoring guidelines in the original English version, scores were categorized as indicative of moderate (20-28 points), or severe depression (≥29 points),[5,6,7]. The Japanese version of the BDI-II has also been validated and the mean score of the Japanese standard population reported as 8.7±6.4,[8], somewhat lower than that of the original English version.

Clinical factors shown in Table 1 were evaluated for each patient and entered into analysis. Clinical severity at study entry was determined by patients and participating

neurologists according to the MG Foundation of America (MGFA) quantitative MG score (QMG),[9], MG activities of daily living scale (MG-ADL),[10] and MG composite scale (MG composite),[11]. Clinical state at study entry following treatment was categorized according to MGFA postintervention status,[9]. The worst condition for each patient was classified according to the MGFA classification,[9]. Prednisone and prednisolone (PSL) are the standard agents for oral corticosteroid therapy in MG and PSL is generally used in Japan. Dose of oral PSL was evaluated for both the current and maximum dosage.

Serum AChR-Ab titers were estimated by radioimmunoassay using ^{125}I-α-bungarotoxin, with levels ≥0.5 nM regarded as positive. MG-specific autoantibodies to voltage-gated potassium channel (Kv1.4-Ab) were detected by immunoprecipitation assay using ^{35}S-labeled cellular extracts as the antigen source, as described elsewhere,[12]. Autoantibodies to titin (titin-Ab) was detected using a commercially available enzyme-linked immunosorbent assay (DLD Diagnostika, Hamburg, Germany). MuSK-Ab was measured using a commercially available radioimmunoprecipitation assay (RSR, Cardiff, UK).

All clinical information and blood samples were obtained after providing informed consent, and the study protocols were approved by the ethics committees of each institute. None of the authors have any conflicts of interest.

Statistics

Correlations between clinical factors and BDI-II score were evaluated using Pearson's correlation for continuous variables or Spearman's rank correlation for categorical variables converted to numerical variables. Factors found to have a value of $p<0.05$ in univariate analysis were entered into multivariate linear regression analysis.

Differences between the two groups were evaluated using the Mann-Whitney U-test

for continuous variables and the χ^2 test for categorical variables. Clinical factors associated with depressive state indicated by BDI-II >21.5 were examined by logistic regression analysis. Clinical factors found to have a value of $p<0.05$ in univariate analysis were entered into multivariate logistic regression analysis to determine background factors independently associated with depressive state.

Values of $p<0.05$ were considered statistically significant. All continuous data are expressed as mean ± standard deviation (SD). Statistical analyses were performed using UNISTAT version 5.6 statistical software (Unistat, London, UK).

RESULTS

Correlations of clinical factors to BDI-II score (Table 1)

Positive correlations to BDI-II score were found for female sex, total QMG, ocular QMG, bulbar QMG, MG composite, MG-ADL, MGFA classification at the worst condition, current dose of PSL, and Improved (I) and Unchanged (U) MGFA postintervention status (Table 1). Negative correlations were seen for AChR-Ab-positivity, and Complete Stable Remission (CSR) and Minimal Manifestations (MM) MGFA postintervention status (Table 1). These clinical factors were entered into multivariate linear regression analysis, which revealed severity (MG composite, p=0.008; MG-ADL, p=0.003) and current dose of PSL (p=0.0002) as factors with independent positive effects on BDI-II total score. However, as mean BDI-II score for the 287 MG patients was 11.0±8.1 and did not differ substantially from and overlapped with that reported as the Japanese standard (8.7±6.4),[8], determining background factors for depressive state in MG using a linear regression model was potentially inappropriate. We therefore conducted further examinations using another regression model.

Table 1. Backgrounds of patients and correlations of clinical factors with BDI-II score (Pearson's correlation or Spearman's rank correlation#)

Clinical factors	*Patient Backgrounds (287 in total)*	Correlation (95% CI)	*P*
Age (years)	*57.5 ± 17.1*	-0.05 (-0.16 – 0.07)	0.200
Female#	*n=193*	0.19 (0.07 – 0.30)	0.001*
Time since onset (years)	*8.9 ± 8.3*	-0.08 (-0.19 – 0.04)	0.10
Age at onset (years)	*48.0 ± 18.6*	-0.01 (-0.13 – 0.10)	0.41
Thymectomy#	*n=141*	0.02 (-0.10 – 0.13)	0.39
Thymoma#	*n=63*	0.06 (-0.05 – 0.18)	0.15
QMG	*7.0 ± 5.1*	0.33 (0.22 – 0.43)	<0.0001*
Ocular QMG	*1.7 ± 1.8*	0.29 (0.17 – 0.39)	<0.0001*
Bulbar QMG	*0.3 ± 0.8*	0.14 (0.02 – 0.25)	0.01*
MG composite	*5.8 ± 5.7*	0.40 (0.30 – 0.50)	<0.0001*
MG ADL	*3.4 ± 3.1*	0.39 (0.29 – 0.49)	<0.0001*
MGFA classification (Worst)#	I/II/III/IV/V: *68/125/60/12/22*	0.17 (0.05 – 0.28)	0.002*
Current dose of PSL (mg/day)	*4.6 ± 5.9*	0.33 (0.22 – 0.43)	<0.0001*
Maximum dose of PSL (mg/day)	*20.5 ± 20.7*	0.02 (-0.09 – 0.14)	0.34
Calcineurin inhibitors#	*n=115*	0.07 (-0.04 – 0.19)	0.10
Crisis#	*n=22*	0.02 (-0.10 – 0.14)	0.38
AChR-Ab positivity#	*n=232*	-0.14 (-0.25 – -0.02)	0.01*
Kv 1.4-Ab positivity#	*n=37*	0.05 (-0.08 – 0.18)	0.22
Titin-Ab positivity#	*n=53*	0.09 (-0.07 – 0.26)	0.10
MuSK-Ab positivity#	*n=2 (of 55 AChR Ab-negative patients)*	Not determined	Not determined
CSR#	*n=21*	-0.10 (-0.22 – 0.01)	0.04*
PR#	*n=22*	-0.09 (-0.20 – 0.03)	0.08
MM#	*n=95*	-0.17 (-0.28 – -0.06)	0.002*
I#	*n=91*	0.12 (0.01 – 0.23)	0.02*
U#	*n=54*	0.13 (0.02 – 0.24)	0.01*
W#	*n=4*	0.03 (-0.08 – 0.15)	0.28

*Variables entered into multivariate regression analysis (see the Results section in the text)

AChR-Ab, antibodies against acetylcholine receptor; CI, confidence interval; CSR, complete stable remission; I, improved; Kv1.4, voltage-gated potassium channel 1.4; MG-ADL, MG activities of daily living scale; MG composite, MG composite scale; MGFA, Myasthenia Gravis Foundation of America; MM, minimal manifestations; MuSK, muscle-specific tyrosine kinase; PR, pharmacologic remission; PSL, prednisolone; QMG, MGFA quantitative MG score; U, unchanged; W, worse.

Factors associated with depressive state (Table 2, 3)

Mean +2 SD for the Japanese standard BDI-II score is 21.5,[8], approximately equal to the cut-off level indicative of moderate or worse depression (BDI-II >20) in the original English version,[5,6,7]. We thus defined BDI-II >21.5 as indicating depressive state, with a frequency of 13.6% (39 of 287) among MG patients in this study. In the present subjects, as no patients showed BDI-II = 21, the total of 39 patients with depressive state using our definition (BDI-II >21.5) was identical to the result we would have achieved if a cut-off of BDI-II >20 had been used. Backgrounds of patients with or without depressive state and comparison between the two groups were shown in Table 2.

Clinical factors associated with depressive state were examined by logistic regression analysis. Factors displaying a value of $p<0.05$ in univariate logistic regression analysis were time since onset, QMG, ocular QMG, MG composite, MG-ADL, current dose of PSL, use of calcineurin inhibitors, and U and Worse (W) MGFA postintervention status (Table 3). These factors were entered into multivariate logistic regression analysis for determination of independent background factors associated with depressive state. Multivariate logistic regression analysis revealed current dose of PSL (odds ratio (OR), 1.09; 95% confidence interval (CI), 1.02-1.17; p=0.01), U of MGFA postintervention status (OR, 3.55; 95%CI,

1.18-10.71; p=0.02), time since onset (OR, 0.93; 95%CI, 0.87-0.99; p=0.03), and MG composite (OR, 1.16; 95%CI, 1.00-1.34; p=0.046) as independent background factors associated with depressive state in MG.

Table 2. Comparison between patients with and without depressive state

Clinical factors	***Patients with depressive state (n=39)***	***Patients without depressive state (n=248)***
Age (years)	*52.3 ± 18.0*	*58.2 ± 16.9*
Female	*n=28*	n=165
Time since onset (years)	*6.1 ± 6.2**	*9.3 ± 8.4*
Age at onset (years)	*46.1 ± 18.7*	*48.3 ± 18.6*
Thymectomy	*n=12*	*n=129*
Thymoma	*n=7*	*n=56*
QMG	*9.9 ± 6.6***	*6.6 ± 4.7*
Ocular QMG	*2.5 ± 2.2**	*1.6 ± 1.7*
Bulbar QMG	*0.5 ± 1.2*	*0.3 ± 0.7*
MG composite	*10.4 ± 7.8****	*5.7 ± 5.5*
MG ADL	*5.3 ± 4.0***	*3.1 ± 2.9*
MGFA classification (Worst)	I/II/III/IV/V: *7/13/14/2/4*	I/II/III/IV/V: *61/112/46/10/18*
Current dose of PSL (mg/day)	*8.1 ± 7.0****	*4.1 ± 5.6*
Maximum dose of PSL (mg/day)	*20.4 ± 21.6*	*20.5 ± 20.6*
Calcineurin inhibitors	*n=19*	*n=96*
Crisis[#]	*n=4*	*n=18*
AChR-Ab positivity	*n=24*	*n=208*
Kv 1.4-Ab positivity	*n=6*	*n=31*
Titin-Ab positivity	*n=8*	*n=45*
CSR	*n=0*	*n=21*
PR	*n=1*	*n=21*
MM	*n=4*	*n=91*
I	*n=11*	*n=80*
U	*n=13*	*n=41*
W	*n=2*	*n=2*

*p<0.05, **p<0.01, ***p<0.001 (Mann-Whitney U-test) compared to patients without depressive state; No significant difference in categorical variables between patients with and without depressive state (χ^2 test)

Table 3. Clinical factors associated with depressive state (univariate logistic regression)

Clinical factors	Odds ratio (95% CI)	*P*
Age (years)	0.98 (0.96 – 1.00)	0.060
Female	1.41 (0.63 – 3.14)	0.41
Time since onset (years)	0.94 (0.89 – 1.00)	0.041*
Age at onset (years)	0.99 (0.97 – 1.01)	0.51
Thymectomy	0.39 (0.18 – 1.24)	0.27
Thymoma	0.91 (0.38 – 2.20)	0.84
QMG	1.12 (1.05 – 1.19)	0.0007*
Ocular QMG	1.26 (1.05 – 1.52)	<0.012*
Bulbar QMG	1.36 (0.94 – 1.98)	0.10
MG composite	1.14 (1.08 – 1.20)	<0.0001*
MG ADL	1.21 (1.09 – 1.35)	0.0003*
MGFA classification (worst)	1.19 (0.88 – 1.62)	0.26
Current dose of PSL (mg/day)	1.09 (1.04 – 1.15)	0.0006*
Maximum dose of PSL (mg/day)	1.00 (0.98 – 1.02)	0.97
Calcineurin inhibitors	2.07 (1.01 – 4.27)	0.048*
Crisis	0.93 (0.26 – 3.29)	0.91
AChR-Ab positivity	1.00 (1.00 – 1.01)	0.28
Kv 1.4-Ab positivity	1.92 (0.70 – 5.26)	0.20
Titin-Ab positivity	1.71 (0.93 – 3.14)	0.10
CSR (no case with BDI-II >21.5)	Not determined	Not determined
PR	0.30 (0.04 – 2.28)	0.24
MM	0.54 (0.24 – 1.24)	0.15
I	1.24 (0.59 – 2.60)	0.57
U	3.14 (1.46 – 6.77)	0.004*
W	5.93 (1.27 – 27.73)	0.023*

*Variables entered into multivariate logistic regression analysis (see the Results section in the

text)

AChR-Ab, antibodies against acetylcholine receptor; CI, confidence interval; CSR, complete stable remission; I, improved; Kv1.4, voltage-gated potassium channel 1.4; MG-ADL, MG activities of daily living scale; MG composite, MG composite scale; MGFA, Myasthenia Gravis Foundation of America; MM, minimal manifestations; MuSK, muscle-specific tyrosine kinase; PR, pharmacologic remission; PSL, prednisolone; QMG, MGFA quantitative MG score; U, unchanged; W, worse.

DISCUSSION

The present study examined associations between detailed parameters of MG and self-reported depressive symptoms and revealed current dose of oral PSL as the most significant background for depressive state in MG. In fact, long-term use of corticosteroids has been suggested to affect the brain and result in the development of depressive conditions,[13-15]. Complications of long-term corticosteroid use emerge at around 10 mg/day of prednisone or PSL,[13-15]. Consistently, mean dose of oral PSL in MG patients with depressive state was 8.1 mg/day, significantly higher than that in patients without depressive state (4.1 mg/day; $p<0.001$ using Mann-Whitney U-test). Although oral corticosteroids represent the first-line and most common agents for immunosuppressive treatment of MG,[16], the present results indicate a possible need for attention to dose and associated depressive side effects. The constant need for medication itself might also cause psychological stress, but use of calcineurin inhibitors (i.e. cyclosporine microemulsion and tacrolimus) was not associated with depressive state. In Japan, oral cyclosporine microemulsion (2.0-5.0 mg/kg/day) was divided into two doses taken at intervals of 12 h, and oral tacrolimus (3.0-4.0 mg/day) was given once a day. There may be some differences of prescription pattern among Japan and

other countries.

BDI-II score for MG patients did not differ substantially from and overlapped with that of the Japanese standard. The frequency of individuals with depressive state (BDI-II >21.5) was 13.6% in this study, lower than that reported by Fisher et al.,[7]. They reported that moderate or worse depression (BDI-II >20 in the original English version) was observed in 33% (15/45) of MG patients,[7]. The frequency of MG patients with depressive symptoms has been inconsistent in previous reports,[1-3]. Anxiety or depressive disorders have been reported as more frequent among patients with MG than in the general population,[4, 17]. Conversely, several authors have found no increased frequency of depression among MG patients compared to the general population,[18-20]. Regarding such discrepancies, given that the present study showed depressive symptoms to be positively correlated with both severity of MG and corticosteroid dose, frequency of depressive MG patients may alter depending on such background factors in subjects.

The present analysis revealed that unchanged status despite treatment and early disease stage are also significant background factors for depressive state, along with disease severity. These findings suggest that achieving early improvement of disease by adequate somatic therapy against MG may be important to avoid a depressive state,[3,18]. Psychiatric symptoms have also been noted to emerge temporarily in exacerbated MG patients, reversing if adequate somatic therapy is given,[3,4].

Lack of formal evaluation of psychopathological characteristics by psychiatrists may represent a limitation to the present study. MG patients have been suggested to exhibit symptoms characteristically similar to the vegetative signs of affective disorders, which may interfere with correct assessment of mood if using only self-rating depression scales,[19,20].

In conclusion, dose of oral corticosteroids appears to represent the major factor

associated with depressive state in MG patients. Unchanged status despite treatment and early disease stage are also significant background factors for depressive state, along with disease severity. Achieving early improvement of disease by adequate MG therapy without long-term use of higher-dose oral corticosteroids may be important to avoiding depressive state in MG patients.

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The contributorship statement:

Dr K Utsugisawa had full access to all of the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis, and certifies all authors to meet the International Committee of Medical Journal Editors (ICMJE) criteria.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Pages 5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Pages 5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pages 5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pages 6-7
Bias	9	Describe any efforts to address potential sources of bias	Page 6
Study size	10	Explain how the study size was arrived at	Pages 5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pages 6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Pages 7-8
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable
		(*c*) Explain how missing data were addressed	Page 6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Not applicable
		(b) Give reasons for non-participation at each stage	Not applicable

		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Page 6; Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	Not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Not applicable
		(*b*) Report category boundaries when continuous variables were categorized	Page 10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	Pages 12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 4 (ARTICLE SUMMARY)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pages 12-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.