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Social disadvantages associated with myasthenia gravis and its treatment: A multicenter cross-sectional study

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ABSTRACT

Objectives: To clarify the social disadvantages associated with myasthenia gravis (MG) and the causal associations with its disease and treatment.

Design: Cross-sectional study.

Setting and Participants: We evaluated 917 consecutive cases of established MG seen at 13 neurological centers in Japan over a short duration.

Outcome measures: All patients completed a questionnaire on social disadvantages resulting from MG and its treatment and a 15-item MG-specific quality of life scale at study entry. Clinical severity at the worst condition was graded according to the MG Foundation of America classification, and that at the current condition was determined according to the quantitative MG score and MG Composite. Maximum dose and duration of dose ≥20mg/day of oral prednisolone during the disease course were obtained from the patients' medical records. Achievement of the treatment target (minimal manifestation status with prednisolone at ≤5 mg/day) was determined at 1, 2, and 4 years after starting treatment and at study entry.

Results: We found that 27.2% of the patients had experienced unemployment, 4.1% had been unwillingly transferred, and 35.9% had experienced a decrease in income, 47.1% of whom reported that the decrease was ≥50% of their previous total income. In addition, 49.0% of the patients reported feeling reduced social positivity. Factors promoting social disadvantages were severity of illness, dose and duration of prednisolone, long-term treatment, and a depressive state and change in appearance after treatment with oral steroids. Early achievement of the treatment target was a major inhibiting factor.

Conclusions: MG patients often experience unemployment, unwilling job transfers, and a decrease in income. In addition, many patients report feeling reduced social positivity. To inhibit the social disadvantages associated with MG and its treatment, a focus needs to be

placed on helping MG patients resume a normal lifestyle as soon as possible by achieving the treatment target.

Strengths and limitations of this study

To elucidate the frequency of unemployment, unwilling job transfers, and reduced income among Japanese patients with MG with various disease statuses while avoiding potential biases, we examined consecutive cases seen at 13 neurological centers.

We statistically and systematically analyzed associations of social disadvantages among MG patients using detailed clinical parameters, including severity of illness, dose and duration of oral steroids, clinical status following treatment, and possible causes based on the patients' self-perceptions.

This study was limited by its cross-sectional design and the fact that it was partially dependent on patients' self-reported data.

INTRODUCTION

Myasthenia gravis (MG) is a neuromuscular disease that used to be considered severe and was associated with a high mortality rate; however, because of current treatments, MG has largely become non-lethal,[1,2]. Still, even today, many MG patients find it difficult to maintain their daily activity levels due to insufficient improvement in disease status, and the long-term side effects of treatment with oral corticosteroids,[2–5], because full remission without steroid treatment is rare in MG,[3,4,6]. Many patients with MG (more than 50% of cross-sectional samples) have insufficient health-related quality of life (HRQOL),[3,4,7–13]. Analyses of detailed clinical data have consistently revealed that not only disease severity, but also oral corticosteroid dose, has significant negative effects on self-perceived HRQOL among patients with MG,[3,4]. The oral corticosteroid dose has been shown to affect items of the MG-QOL15, a 15-item MG-specific QOL scale,[14,15], associated with social or community mobility,[4]. It is possible that side effects resulting from treatment with corticosteroids, such as problems associated with appearance or a depressive state, negatively affect personal relationships, positive thinking, and social activities,[4,16].

Many patients with MG cannot fully participate in social activities due to the effects of the disease and its treatment,[4,9–13]. These patients therefore appear to suffer social disadvantages such as unemployment and a decrease in income, which can lead to a lower HRQOL,[9–11,13]. However, information regarding the prevalence of these disadvantages and their detailed associations with MG remains scarce. Therefore, we conducted a cross-sectional questionnaire survey to obtain information on social disadvantages experienced by patients with MG. We also examined possible associations with detailed clinical parameters.

PATIENTS AND METHODS

Patients

This study was conducted at 13 neurological centers (Japan MG Registry Group, see Table 1) in Japan. We evaluated patients with established MG between April and July 2015. To avoid potential bias, we enrolled consecutive patients with various disease statuses over a short duration (4 months). During this period, we collected complete clinical data, including present disease status, past course of MG Foundation of America (MGFA) postintervention status, and current and past treatment regimens, from 923 of 1,088 patients with MG who visited our hospitals. Among these 923 patients, 917 responded to a questionnaire we conducted on social disadvantages resulting from MG and its treatment (Fig. 1), provided written informed consent, and underwent analysis.

The diagnosis of MG was based on clinical findings (fluctuating symptoms with easy fatigability and recovery after rest) with amelioration of symptoms after intravenous administration of anticholinesterase, decremental muscle response to a train of low-frequency repetitive nerve stimuli of 3 Hz, or the presence of autoantibodies specific for the acetylcholine receptor (AChR) of skeletal muscle (AChR-Ab) or for muscle-specific tyrosine kinase (MuSK-Ab).

Table 1. Institutions participating in the Japan MG Registry Study 2015

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MG, myasthenia gravis.

Questionnaire on social disadvantages resulting from MG and its treatment

In the present questionnaire survey (Fig. 1), we first elucidated whether each patient had experienced unemployment, an unwilling job transfer, and/or a decrease in income (Fig. 1A, items 1–3). For the patients who had experienced a decrease in income, we further asked to what degree their previous total income had decreased (Fig. 1A, item 4). We also asked whether the patients felt that their social positivity and activity had declined due to MG and/or its treatment (Fig. 1A, item 5). Only social disadvantages after disease onset were taken into account.

For the patients who answered “yes” for any of the question items 1–3 or 5 (Fig. 1A), we then asked to what degree (0–3) they thought that each of the 12 items were possible causes of their experienced social disadvantages (Fig. 1B, items 1–12). Correlations between the degree (0–3) of each of the 12 items and each social disadvantage were then calculated (Table 2).

Table 2. Associations between question items and social disadvantages (Spearman rank correlation)

Question item	Correlation (95%CI) with social disadvantages, p-value		
	Unemployment or unwilling transfer (213/486 cases)	Decrease in income (244/486 cases)	Reduced social positivity (449/486 cases)
1. Insufficient control of symptoms	**0.19 (0.095 – 0.285), <0.0001**	0.08 (−0.01 – 0.18), 0.05	0.05 (−0.04 – 0.14), 0.13
2. Depressive state, changes in mood or character after PSL (PSL use, 81% of subjects)	0.10 (0.00 – 0.19), 0.03	0.02 (−0.08 – 0.12), 0.36	**0.20 (0.10 – 0.28), <0.0001**
3. Changes in appearance after PSL (PSL use, 81% of 486 subjects)	0.07 (−0.03 – 0.16), 0.10	0.05 (−0.05 – 0.15), 0.14	**0.20 (0.11 – 0.28), <0.0001**
4. Diabetes mellitus, osteoporosis, cataracta and/or other arteriosclerotic diseases (PSL use, 81% of subjects)	0.05 (−0.05 – 0.15), 0.16	0.13 (0.03 – 0.22), 0.006	0.12 (0.03 – 0.21), 0.005
5. Side effects related to non-steroid immunosuppressive agents (CNI use, 53%; AZA use, 5%)	−0.02 (−0.12 – 0.07), 0.31	0.05 (−0.05 – 0.15), 0.16	0.08 (−0.01 – 0.17), 0.04
6. Adverse events related to plasmapheresis (28%)	0.04 (−0.06 – 0.14), 0.21	0.07 (−0.03 – 0.17), 0.08	0.04 (−0.05 – 0.13), 0.20
7. Adverse events related to intravenous immunoglobulin (16%)	0.05 (−0.05 – 0.15), 0.17	0.07 (−0.03 – 0.17), 0.08	0.06 (−0.03 – 0.15), 0.08

8. Long-term (>1 month) hospital stay	**0.20 (0.10 – 0.29), <0.0001**	**0.27 (0.19 – 0.37), <0.0001**	−0.05 (−0.14 – 0.04), 0.12
9. Short-term (≤1 week) hospital stay	0.12 (0.02 – 0.24), 0.006	0.13 (0.04 – 0.23), 0.003	0.09 (0.00 – 0.17), 0.03
10. Need to go to the hospital for years	**0.16 (0.07 – 0.26), <0.001**	**0.15 (0.06 – 0.25), <0.001**	0.03 (−0.06 – 0.12), 0.25
11. Need to take various oral drugs for years	0.05 (−0.05 – 0.15), 0.16	0.07 (−0.03 – 0.16), 0.10	0.13 (0.04 – 0.21), 0.002
12. Bias for intractable and uncommon diseases from others	**0.16 (0.06 – 0.26), <0.001**	0.02 (−0.08 – 0.12), 0.35	**0.21 (0.12 – 0.30), <0.0001**

Significant correlations are indicated bold font. AZA, azathioprine; CI, confidence interval; CNI, calcineurin inhibitor; PSL, prednisolone.

Clinical factors from examinations and records

As shown in Table 3, clinical factors were evaluated for each patient and entered into correlation analysis with the social disadvantages. Clinical severity at the worst condition was classified according to MGFA classifications,[17], and in some patients (792/917), was determined according to the quantitative MG score (QMG),[17] from medical records. Clinical severity at the current condition was determined according to QMG and the MG Composite (MGC),[18,19]. All patients completed the Japanese version of the MG-QOL15 (MG-QOL15-J),[3] at study entry. Clinical status following treatment was categorized according to MGFA postintervention status,[17]. Previously, minimal manifestations (MM) or better status with prednisolone (PSL) at ≤5 mg/day (MM or better-5 mg) was identified as a practical treatment target,[3,4], as the HRQOL of patients with this status was reported to be as good as that of complete stable remission (CSR),[3,4]. This category grouping into MM or better status (i.e., MM, pharmacological remission (PR) or CSR) and a cut-off of the PSL dose at 5 mg/day were proposed according to the results of a previous decision tree analysis for good HRQOL,[3]. The achievement of MM or better-5 mg lasting more than 6 months was determined at 1, 2, and 4 years into treatment and at study entry. The maximum and current dose of oral PSL and the duration of oral PSL ≥20 mg/day were obtained from the patients' medical records.

Serum AChR-Ab titers were estimated by radioimmunoassay using ^{125}I-α-bungarotoxin, and levels ≥0.5 nM were regarded as positive. MuSK-Ab was measured using a commercially available radioimmunoprecipitation assay (RSR, Cardiff, UK).

The study protocols were approved by the ethics committees of each participating institution. Written informed consent was obtained from all patients participating in the study.

Table 3. Patient characteristics and associations between clinical factors and social disadvantages (Spearman rank correlation)

Clinical factor	Mean ± standard deviation (range) *(n=917)*	Correlation (95%CI) with social disadvantages, p-value		
		Unemployment or unwilling transfer (213/680 cases)	Decrease in income (244/680 cases)	Reduced social positivity (449/917 cases)
Age, yrs	57.1 ± 15.4 (19–93)	-0.08 (-0.16 – −0.01), 0.02	−0.07 (−0.14 – 0.01), 0.04	0.00 (−0.07 – 0.07), 0.49
Female (%)	65.2 (598/917)	0.11 (0.00 – 0.18), 0.02	0.01 (−0.06 – 0.09), 0.39	**0.17 (0.10 – 0.24), <0.0001**
Time since onset, yrs	11.9 ± 10.7 (0.1–83)	0.08 (0.00 – 0.15), 0.02	-0.01 (−0.08 – 0.07), 0.43	0.00 (−0.07 – 0.08), 0.45
Age at onset, yrs	45.4 ± 18.1 (3–91)	-0.11 (−0.18 – -0.04), 0.0025	-0.04 (−0.12 – 0.03), 0.12	-0.03 (−0.10 – 0.04), 0.22
Thymectomy, %	52.4 (482/917)	**0.18 (0.10 – 0.25), <0.0001**	**0.21 (0.13 – 0.28), <0.0001**	0.12 (0.05 – 0.19), 0.0003
Thymoma, %	25.0 (230/917)	0.01 (−0.09 – 0.10), 0.46	0.05 (−0.05 – 0.15), 0.15	0.01 (−0.08 – 0.11), 0.38
AChR-Ab-positivity, %	81.1 (744/917)	−0.08 (−0.16 – −0.01), 0.02	−0.08 (−0.16 – −0.01), 0.01	-0.05 (−0.12 – 0.02), 0.07
MuSK-Ab-positivity, %	2.5 (23/917)	0.12 (0.00 – 0.23), 0.03	0.07 (−0.05 – 0.18), 0.14	0.09 (−0.03 – 0.20), 0.07
MGFA classification (Worst)	I/II/III/IV/V 208/392/186/37/94	**0.28 (0.21 – 0.35), <0.0001**	**0.31 (0.24 – 0.38), <0.0001**	**0.22 (0.15 – 0.28), <0.0001**
Bulbar symptoms, % (Worst)	49.4 (453/917)	**0.17 (0.10 – 0.25), <0.0001**	**0.18 (0.10 – 0.25), <0.0001**	0.13 (0.06 – 0.20), 0.0002
Worst QMG (n=792)	13.5 ± 7.5 (1–39)	**0.26 (0.18 – 0.33), <0.0001**	**0.32 (0.24 – 0.39), <0.0001**	**0.25 (0.17 – 0.32), <0.0001**
Current QMG	6.6 ± 4.9 (0–29)	**0.20 (0.13 – 0.27), <0.0001**	**0.20 (0.12 – 0.27), <0.0001**	**0.27 (0.20 – 0.34), <0.0001**
Current MGC	4.3 ± 5.2 (0–32)	**0.21 (0.14 – 0.28), <0.0001**	**0.21 (0.13 – 0.28), <0.0001**	**0.28 (0.22 – 0.35), <0.0001**

Current MG-QOL15-J	13.8 ± 13.2 (0–60)	0.35 (0.28 – 0.41), <0.0001	0.34 (0.27 – 0.40), <0.0001	0.48 (0.43 – 0.54), <0.0001
Peak dose of PSL, mg/day	22.0 ± 19.6 (0–80)	**0.16 (0.88 – 0.24), <0.0001**	**0.22 (0.15 – 0.30), <0.0001**	0.08 (0.01 – 0.15), 0.0143
Duration of PSL ≥20 mg/day, yrs	0.72 ± 1.7 (0–19.6)	**0.19 (0.11 – 0.27), <0.0001**	**0.22 (0.14 – 0.30), <0.0001**	**0.15 (0.07 – 0.22), <0.0001**
Current dose of PSL, mg/day	4.4 ± 5.0 (0–40.0)	0.11 (0.03 – 0.19), 0.003	0.12 (0.05 – 0.20), 0.0011	0.11 (0.04 – 0.18), 0.002
MM or better with 5 mg at 1 year into treatment, %	34.0 (299/880)	**-0.17 (−0.24 – −0.09), <0.0001**	**-0.17 (−0.25 – −0.09), <0.0001**	**-0.19 (−0.26 – −0.11), <0.0001**
MM or better with 5 mg at 2 years into treatment, %	40.5 (298/735)	-0.15 (−0.24 – −0.07), 0.0002	-0.12 (-0.21 – -0.04), 0.003	**-0.17 (−0.25 – −0.09), <0.0001**
MM or better with 5 mg at 4 years into treatment, %	46.1 (236/512)	**−0.20 (−0.29 – −0.11), <0.0001**	**-0.17 (−0.26 – −0.08), <0.0001**	**-0.23 (−0.31 – −0.15), <0.0001**
MM or better with 5 mg at present, %	48.9 (448/917)	**−0.17 (−0.24 – −0.10), <0.0001**	**−0.15 (−0.23 – −0.08), <0.0001**	**−0.22 (-0.30 – −0.16), <0.0001**

Significant correlations are indicated bold font. AChR-Ab, antiacetylcholine receptor antibody; CI, confidence interval; MGC, Myasthenia Gravis Composite; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MG-QOL15, 15-item MG-specific quality of life scale; MG-QOL15-J, Japanese version of the MG-QOL15; MM, minimal manifestations; MuSK-Ab, muscle-specific kinase antibody; PSL, prednisolone; QMG, MGFA quantitative MG score.

Statistical analysis

Associations between various clinical parameters and experiences of social disadvantages were evaluated using Spearman rank correlations. Some factors that showed a significant correlation in univariate analysis were entered into multivariate logistic regression analysis to determine the parameters most significantly associated with social disadvantages. All continuous data are expressed as the mean ± standard deviation and range (min–max). Statistical analyses were performed using UNISTAT version 5.6 (Unistat, London, UK).

RESULTS

Frequency of social disadvantages resulting from MG and its treatment

Among the 917 MG patients who answered our questionnaire survey, 237 responded "not applicable (did not receive income from employment)" for the question items shown in Figure 1, A1–3. After excluding these patients, 185 (27.2%) out of the remaining 680 answered "I have experienced unemployment", 28 (4.1%) answered "I have experienced an unwilling job transfer", and 244 (35.9%) answered "I have experienced a decrease in income". Out of 244 who reported experiencing a decrease in income, 115 (47.1%) answered that the decrement in total income was ≥50%.

Among the 917 total patients, 449 (49.0%) answered "My social positivity and activity were reduced", and 486 answered "yes" for at least one of question items in Figure 1, A1–3, and 5. The experiences of unemployment or unwilling job transfer and that of a decrease in income showed significant correlations to the perception of reduced social positivity and activity ($r=0.35$, $p<0.0001$; $r=0.35$, $p<0.0001$) (Spearman rank correlation).

Possible causes perceived by patients and correlations with social

disadvantages

Correlations between social disadvantages and the degree (0–3) to which the 486 applicable patients felt each of 12 question items in Figure 1B were possible causes of these disadvantages are shown in Table 2.

The items that exhibited significant positive correlations ($p<0.001$, $r\geq0.15$) to the "experience of unemployment or unwilling job transfer" were: "an insufficient control of MG symptoms"; "long-term (>1 month) hospital stay for treatment"; "need to go to the hospital for years"; and "bias for intractable and uncommon diseases from others". Significant positive correlations with "experience of a decrease in income" were "long-term (>1 month) hospital stay for treatment" and "need to go to hospital for years", and those with "reduced social positivity and activity" were "depressive state, changes in mood or character after oral corticosteroids", "changes in appearance after oral corticosteroids", and "bias for intractable and uncommon diseases from others".

Clinical parameters and correlations with social disadvantages

The backgrounds of the 917 patients and correlations of clinical parameters with the experience of social disadvantages (in applicable patients) are shown in Table 3.

In 680 patients who received income from employment, the clinical parameters that exhibited significant positive correlations ($p <0.0001$, $r \geq0.15$) with "experience of unemployment or unwilling job transfer" and with "experience of a decrease in income" were identical; these were: thymectomy; severity at worst condition (MGFA classification, bulbar symptoms, QMG); severity at current condition (QMG, MGC); peak dose of PSL; and duration of PSL ≥20 mg/day. Conversely, achieving MM or better-5 mg at 1 and 4 years into treatment and at present exhibited significant negative correlations ($p<0.0001$, $r\leq-0.15$).

In the 917 patients, the clinical parameters that exhibited significant positive correlations ($p<0.0001$, $r\geq0.15$) with "reduced social positivity and activity" were: female sex; severity at worst condition (MGFA classification, QMG); severity at current condition (QMG, MGC); and duration of PSL ≥20 mg/day. Achieving MM or better-5 mg at any time point exhibited a significant negative correlation ($p<0.0001$, $r\leq-0.15$) to this adverse effect.

To elucidate which time point of achieving MM or better-5 mg was most significant in inhibiting each of these social disadvantages, multivariate logistic regression analysis was performed using parameters that showed negative correlations as variables. We found that "at 4 years into treatment" was the most significant time point for achieving MM or better-5 mg in regard to inhibiting "experience of unemployment or unwilling job transfer" (odds ratio [OR], 0.61; p=0.03), "experience of a decrease in income" (OR, 0.61; p=0.04), and "reduced social positivity and activity" (OR, 0.49; p=0.005).

Current MG-QOL15-J scores correlated positively with each of these social disadvantages (underlined in Table 3), suggesting that the current HRQOL of the patients was worse with such experiences.

DISCUSSION

The questionnaire results demonstrated that unemployment or an unwilling job transfer after MG onset was experienced by 31.3% of the patients, and a decrease in income was experienced by 35.9%, among whom, 47.1% reported a decrease in total income of more than 50%. In a large German MG cohort, 21.0% of the patients experienced hardships in their jobs, and 28.3% were forced to retire early due to MG,[9]. In a study in Thailand, the unemployment rate among MG patients was 26–58%, and reduced income was seen in 43–48%,[10]. In a community-based survey of Australian MG patients, 39.4% had been forced to

stop working due to MG, and 19.4% had to change their occupation,[13]. Only 40.6% of that cohort was working at the time of the survey, and the rest were unable to work due to the effects of the disease,[13]. Although the socioeconomic environments of these patients likely differ to some degree, no substantial differences were observed in the frequency of such disadvantages between these countries. Therefore, a substantial number of MG patients are burdened with socioeconomic disadvantages. MG may not be a major public health problem in terms of the number of patients affected; however, in terms of chronic problems due to its lifelong status, MG may have a substantial impact not only on the patients themselves, but also on the community,[9].

The causes of these social disadvantages perceived by the patients themselves included bias from others, as well as an insufficient control of symptoms and long-term treatment (hospital stay >1 month and visiting the hospital for years). In many instances, the manifestations of MG are much more evident to the patient than to others, and appear to be frequently misunderstood,[20]. Fatigue is a very common symptom in MG, and this can be misinterpreted for laziness in the context of the workplace. Among individuals who have work demands and other responsibilities, such underestimations of MG symptoms interfere with performing social needs,[9,11]. Efforts must be made to help patients with MG achieve early improvement and return to a normal lifestyle as soon as possible,[3,4,6]. Efforts must also be made to better inform the public (particularly employers) about the characteristics of MG symptoms, as fluctuating weakness with fatigability which can be often underestimated at the workplace.

Participation in work is important not only because of financial resources and access to benefits that jobs provide (e.g., health insurance and welfare), but also because of a person's sense of self-respect, social network, and feelings of usefulness and

satisfaction,[21,22]. While at work, individuals are stimulated by physical and mental activities,[9]. Job loss is reportedly associated with worse self-perceived HRQOL and increased adverse health behaviors,[22]. In the patients with MG in the present study, experiences of unemployment or unwilling jobs transfers were consistently significantly correlated with the perception of reduced social positivity and low HRQOL scores. Adjustments in the workplace, as well as adequate therapy, are therefore important for patients with MG,[9].

Physical disability is naturally linked to occupational status and the likelihood of losing one's job. However, among the clinical parameters taken from examinations and patient records in the present study, both severity of illness (worst and current status) and dose of oral steroids (peak dose of PSL and duration of PSL ≥20 mg/day) were positively correlated with "unemployment or an unwilling job transfer" and "a decrease in income". Such associations are consistent with previous reports in which both severity of illness and dose of oral steroids were the most significant factors negatively affecting patients' HRQOL,[3,4]. The severity of the disease tends to affect personal mobility, while the dose of oral steroids tends to affect social mobility,[4]; both of these disadvantages naturally lead to unemployment and a decrease in income.

On the other hand, strangely, thymectomy appeared to positively correlate with both "unemployment or an unwilling job transfer" and "a decrease in income". These unexpected associations were likely due to correlations between thymectomy and other disadvantage-promoting factors such as "long-term (>1 month) hospital stay for treatment" ($r=0.27$, $p<0.0001$)", peak dose of PSL ($r=0.37$, $p<0.0001$), and duration of PSL ≥20 mg/day ($r=0.37$, $p<0.0001$) (Spearman rank correlation). These correlations might have arisen from previous treatment methods in some Japanese institutions in which thymectomy was often followed by

high-dose oral steroid therapy utilizing dose escalation and de-escalation. In actuality, performing thymectomy itself is considered to have no direct effect on HRQOL,[10–12] or the social disadvantages of patients with MG.

Achieving MM or better-5 mg likely enables patients to live a normal lifestyle without having to worry about complications resulting from steroids,[3,4], and the achievement of such status negatively correlates with social disadvantages. Interestingly, among 1, 2, and 4 years into treatment and at present, 4 years into treatment appeared to be the most significant time point for inhibiting social disadvantages. The critical time for control of MG is reported to encompass the first several years after onset,[2], and the first 4 years or so into treatment may be a permissible limit to achieve sufficient disease control that leads to a good long-term condition. Alternatively, for employers, a permissible employment time for patients who have uncontrolled illness and/or are experiencing treatment-related side effects may be limited to the first several years after disease onset. In any case, an early return to a normal lifestyle at least within the first several years of treatment may be important.

Among all patients, 49.0% answered that their "social positivity and activity was reduced", and the self-perceived main causes included "depressive state, changes in mood or character after oral corticosteroids", and "changes in appearance after oral corticosteroids". The most significant clinical factor promoting a depressive state in patients with MG is reportedly an insufficient reduction in the dose of long-term oral steroids,[16]. It is probable that in the patients taking high doses of oral steroids, the problems in appearance and depressive state negatively affect personal relationships, positive thinking, and social activities,[4]. Therefore, for long-term use, oral corticosteroids should be given at the lowest possible dose,[3,4,16,23]. Bias from others and female sex were also associated with decreased social positivity. Therefore, adequate social support, public acceptance, and

understanding may be highly beneficial in improving life circumstances among patients with MG,[9,11].

In conclusion, although this study was limited by the fact that it was partially dependent on patients' self-reported data, among MG patients receiving income from employment in Japan, unemployment or an unwilling job transfer after MG onset was experienced by 31.3%, and a decrease in income by 35.9%, among whom, 47.1% experienced a decrease in total income of more than 50%. Among all patients with MG, 49.0% perceived a reduction in their social positivity. Severity of illness, dose and duration of PSL, long-term treatment, and a depressive state and changes in appearance after oral steroids are factors promoting such disadvantages. An early return to a normal lifestyle without corticosteroid complications (e.g., MM or better-5 mg) is therefore considered a major factor inhibiting such disadvantages. It is also important that employers and coworkers have better informed perceptions about MG, and that patients' workplace or living surroundings help accommodate MG symptoms.

Contributorship statement

Study concept and design: Y Nagane, H Murai, T Imai, N Kawaguchi, M Masuda, M Aoki and K Utsugisawa.

Acquisition of data: Y Nagane, H Murai, T Imai, D Yamamoto, E Tsuda, N Minami, Y Suzuki, T Kanai, A Uzawa, N Kawaguchi, M Masuda, S Konno, H Suzuki, M Aoki and K Utsugisawa.

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Competing interests

Dr. Y. Nagane reports no disclosures. Dr. H. Murai reports no disclosures. Dr. T. Imai reports no disclosures. Dr. D. Yamamoto reports no disclosures. Dr. E. Tsuda reports no disclosures. Dr. N. Minami reports no disclosures. Dr. Y. Suzuki reports no disclosures. Dr. T. Kanai reports no disclosures. Dr. A. Uzawa reports no disclosures. Dr. N. Kawaguchi reports no disclosures. Dr. M. Masuda reports no disclosures. Dr. S. Konno reports no disclosures. Dr. H. Suzuki reports no disclosures. Dr. M. Aoki reports no disclosures. Dr. K. Utsugisawa reports no disclosures.

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Data sharing statement

No additional data are available.

REFERENCES

1. Gilhus NE. Autoimmune myasthenia gravis. *Expert Rev Neurother* 2009;9:351–358.
2. Grob D, Brunner N, Namba T, et al. Lifetime course of myasthenia gravis. *Muscle Nerve* 2008;37:141–149.
3. Masuda M, Utsugisawa K, Suzuki S, et al. The MG-QOL15 Japanese version: validation and associations with clinical factors. *Muscle Nerve* 2012;46:166–173.
4. Utsugisawa K, Suzuki S, Nagane Y, et al. Health-related quality-of-life and treatment targets in myasthenia gravis. *Muscle Nerve* 2014;50:493–500.
5. Pascuzzi RM, Coslett HB, Johns TR. Long-term corticosteroid treatment of myasthenia gravis: report of 116 patients. *Ann Neurol* 1984;15:291–298.
6. Sanders DB, Evoli A. Immunosuppressive therapies in myasthenia gravis. *Autoimmunity* 2010;43:428–435.
7. Padua L, Evoli A, Apirile I, et al. Health-related quality of life in patients with myasthenia gravis and the relationship between patient-oriented assessment and conventional measurements. *Neurol Sci* 2001;22:363–369.
8. Paul RH, Nash JM, Cohen RA, et al. Quality of life and well-being of patients with myasthenia gravis. *Muscle Nerve* 2001;24:512–516.
9. Twork S, Wiesmeth S, Klewer J, et al. Quality of life and life circumstances in German myasthenia gravis patients. *Health Qual Life Outcomes* 2010;8:129.
10. Kulkantrakorn K, Sawanyawisuth K, Tiamkao S. Factors correlating quality of life in patients with myasthenia gravis. *Neurol Sci* 2010;31:571–573.
11. Basta IZ, Pekmezović TD, Perić SZ, et al. Assessment of health-related quality of life in patients with myasthenia gravis in Belgrade (Serbia). *Neurol Sci* 2012;33:1375–1381.
12. Boldingh MI, Dekker L, Maniaol AH, et al. An up-date on health-related quality of life in

myasthenia gravis -results from population based cohorts. *Health Qual Life Outcomes* 2015;13:115.

13. Blum S, Lee D, Gillis D, et al. Clinical features and impact of myasthenia gravis disease in Australian patients. *J Clin Neurosci* 2015;22:1164–1169.

14. Burns TM, Conaway MR, Cutter GR, et al. Less is more, or almost as much: a 15-item quality-of-life instrument for myasthenia gravis. *Muscle Nerve* 2008;38:957–963.

15. Burns TM, Grouse CK, Conaway MR, et al.Construct and concurrent validation of the MG-QOL15 in the practice setting. *Muscle Nerve* 2010;41:219–226.

16. Suzuki Y, Utsugisawa K, Suzuki S, et al. Factors associated with depressive state in patients with myasthenia gravis: a multicenter cross-sectional study. *BMJ Open* 2011;1:e000313.

17. Jaretzki A 3rd, Barohn RJ, Ernstoff RM, 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* 2000;55:16–23.

18. Burns TM, Conaway MR, Cutter GR, et al. Construction of an efficient evaluative instrument for myasthenia gravis: the MG composite. *Muscle Nerve* 2008;38:1553–1562.

19. Burns TM, Conaway M, Sanders DB, et al. The MG composite: A valid and reliable outcome measure for myasthenia gravis. *Neurology* 2010;74:1434–1440.

20. Burns TM. History of outcome measures for myasthenia gravis. *Muscle Nerve* 2010;42:5–13.

21. Gignac MA, Lacaille D, Beaton DE, et al. Striking a balance: Work-health-personal life conflict in women and men with arthritis and its association with work outcomes. *J Occup Rehabil* 2014;24: 573–584.

22. van der Hiele K, van Gorp DA, Heerings MA, et al. The MS@Work study: a 3-year

prospective observational study on factors involved with work participation in patients with relapsing-remitting Multiple Sclerosis. *BMC Neurol* 2015;15:134.

23. Nagane Y, Suzuki S, Suzuki N, et al. Early aggressive treatment strategy against myasthenia gravis. *Eur Neurol* 2011;65:16–22.

Questionnaire for investigating the social disadvantages associated with myasthenia gravis and its treatment

JAMG-R ID:_____

(A) Regarding the social disadvantages resulting from myasthenia gravis (MG) and/or its treatment to date,

1. I have experienced unemployment---------- (1 yes; 0 no; or *not applicable)
2. I have experienced an unwilling job transfer---------- (1 yes; 0 no; or *not applicable)
3. I have experienced a decrease in income---------- (1 yes; 0 no; or *not applicable)
   4. If yes, what is the percentage of the decrease in the total income?
   ------- (1. <10%, 2. 10–25%, 3. 25–50%, 4. ≥50%)
5. I feel as though my social positivity and activity has declined---------- (1 yes; 0 no)

(B) If you answered "yes" to any of the questions above, to what degree is each of the items below (1–12) related to the cause?

Please select the degree of the relationship from the following:

0) Not related at all; 1) May be related; 2) Related to some degree; or 3) Strongly related

1. An insufficient control of MG symptoms----------(0; 1; 2; 3.)
2. Depressive state, or changes in mood or character after oral corticosteroids
   ----------(0; 1; 2; 3; or *I did not take oral steroids)
3. Changes in appearance after oral corticosteroids---------(0; 1; 2; 3; or *I did not take oral steroids)
4. Side effects of steroids such as diabetes mellitus, osteoporosis, cataracta and/or other arteriosclerotic diseases----------(0; 1; 2; 3; or *I did not take oral steroids)
5. Side effects of non-steroid immunosuppressive agents---(0; 1; 2; 3; or *I did not take such drugs)
6. Adverse events related to plasmapheresis----------(0; 1; 2; 3; or *I did not receive plasmapheresis)
7. Adverse events related to intravenous immunoglobulin-
   ----------(0; 1; 2; 3; or *I did not receive immunoglobulin)
8. Long-term (>1 month) hospital stay for treatment---------- (0; 1; 2; 3)
9. Short-term (≤1 week) hospital stay for treatment---------- (0; 1; 2; 3)
10. Need to go to the hospital for years---------- (0; 1; 2; 3)
11. Need to take various oral drugs continuously for years---------- (0; 1; 2; 3)
12. Bias for intractable and uncommon diseases from others---------- (0; 1; 2; 3)

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	Pages 1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 6
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 7-13
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pages 7-13
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 7-13
Bias	9	Describe any efforts to address potential sources of bias	Page 7
Study size	10	Explain how the study size was arrived at	Page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pages 7-13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 14
		(*b*) Describe any methods used to examine subgroups and interactions	Pages 7-14
		(*c*) Explain how missing data were addressed	Page 7
		(*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	Pages 14-16
		(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	Pages 12-13
		(b) Indicate number of participants with missing data for each variable of interest	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	Page 16
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*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	Page 16-19
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 20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 16-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pages 16-17
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 2

*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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Social disadvantages associated with myasthenia gravis and its treatment: A multicenter cross-sectional study

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Social disadvantages associated with myasthenia gravis and its treatment: A multicenter cross-sectional study

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ABSTRACT

Objectives: To clarify the social disadvantages associated with myasthenia gravis (MG) and examine associations with its disease and treatment.

Design: Cross-sectional study.

Setting and Participants: We evaluated 917 consecutive cases of established MG seen at 13 neurological centers in Japan over a short duration.

Outcome measures: All patients completed a questionnaire on social disadvantages resulting from MG and its treatment and a 15-item MG-specific quality of life scale at study entry. Clinical severity at the worst condition was graded according to the MG Foundation of America classification, and that at the current condition was determined according to the quantitative MG score and MG Composite. Maximum dose and duration of dose ≥20mg/day of oral prednisolone during the disease course were obtained from the patients' medical records. Achievement of the treatment target (minimal manifestation status with prednisolone at ≤5 mg/day) was determined at 1, 2, and 4 years after starting treatment and at study entry.

Results: We found that 27.2% of the patients had experienced unemployment, 4.1% had been unwillingly transferred, and 35.9% had experienced a decrease in income, 47.1% of whom reported that the decrease was ≥50% of their previous total income. In addition, 49.0% of the patients reported feeling reduced social positivity. Factors promoting social disadvantages were severity of illness, dose and duration of prednisolone, long-term treatment, and a depressive state and change in appearance after treatment with oral steroids. Early achievement of the treatment target was a major inhibiting factor.

Conclusions: MG patients often experience unemployment, unwilling job transfers, and a decrease in income. In addition, many patients report feeling reduced social positivity. To inhibit the social disadvantages associated with MG and its treatment, a focus needs to be

placed on helping MG patients resume a normal lifestyle as soon as possible by achieving the treatment target.

Strengths and limitations of this study

To avoid inclusion biases, we examined consecutive cases.

We systematically analyzed associations of social disadvantages among a large number of MG patients using detailed clinical parameters.

This study was limited by its cross-sectional and partly retrospective design and the fact that it was dependent on patients' self-reported data.

INTRODUCTION

Myasthenia gravis (MG) is a neuromuscular disease that used to be considered severe and was associated with a high mortality rate; however, because of current treatments, MG has largely become non-lethal,[1,2]. Still, even today, many MG patients find it difficult to maintain their daily activity levels due to insufficient improvement in disease status, and the long-term side effects of treatment with oral corticosteroids,[2–5], because full remission without steroid treatment is rare in MG,[3,4,6]. Health-related quality of life (HRQOL) is reduced in many patients with MG,[3,4,7–13]. Analyses of detailed clinical data have consistently revealed that not only disease severity, but also oral corticosteroid dose, has significant negative effects on self-perceived HRQOL among patients with MG,[3,4]. The oral corticosteroid dose has been shown to affect items of the MG-QOL15, a 15-item MG-specific QOL scale,[14,15], associated with social or community mobility,[4]. It is possible that side effects resulting from treatment with corticosteroids, such as problems associated with appearance or a depressive state, negatively affect personal relationships, positive thinking, and social activities,[4,16].

Many patients with MG cannot fully participate in social activities due to the effects of the disease and its treatment,[4,9–13]. These patients therefore appear to suffer social disadvantages such as unemployment and a decrease in income, which can lead to a lower HRQOL,[9–11,13]. However, information regarding the prevalence of these disadvantages and their detailed associations with MG remains scarce. Therefore, we conducted a cross-sectional questionnaire survey to obtain information on social disadvantages experienced by patients with MG. We also examined possible associations with detailed clinical parameters.

PATIENTS AND METHODS

Patients

This study was conducted at 13 neurological centers (Japan MG Registry Group, see Supplementary Table 1) in Japan. We evaluated patients with established MG between April and July 2015. To avoid potential bias, we enrolled consecutive patients with various disease statuses over a short duration (4 months). During this period, a total of 1088 MG patients visited our hospitals. From this group we were able to collect full detailed clinical data from 923 patients, and 165 were excluded from the study because of insufficient data collection. Data collected included present disease status, past course of MG Foundation of America (MGFA) postintervention status, and current and past treatment regimens. Among these 923 patients, 917 responded completely to a questionnaire we conducted on social disadvantages resulting from MG and its treatment (Fig. 1), provided written informed consent, and underwent analysis.

The diagnosis of MG was based on clinical findings (fluctuating symptoms with easy fatigability and recovery after rest) with amelioration of symptoms after intravenous administration of anticholinesterase, decremental muscle response to a train of low-frequency repetitive nerve stimuli of 3 Hz, or the presence of autoantibodies specific for the acetylcholine receptor (AChR) of skeletal muscle (AChR-Ab) or for muscle-specific tyrosine kinase (MuSK-Ab).

Questionnaire on social disadvantages resulting from MG and its treatment

In the present questionnaire survey (Fig. 1), we first elucidated whether each patient had experienced unemployment, an unwilling job transfer, and/or a decrease in income (Fig. 1A, items 1–3). For the patients who had experienced a decrease in income, we further asked

to what degree their previous total income had decreased (Fig. 1A, item 4). We also asked whether the patients felt that their social positivity and activity had declined due to MG and/or its treatment (Fig. 1A, item 5). Only social disadvantages after disease onset were taken into account.

For the patients who answered "yes" for any of the question items 1–3 or 5 (Fig. 1A), we then asked to what degree (0–3) they thought that each of the 12 items were possible causes of their experienced social disadvantages (Fig. 1B, items 1–12). Correlations between the degree (0–3) of each of the 12 items and each social disadvantage were then calculated (Table 1). This questionnaire was newly developed for this survey.

Table 1. Associations between question items and social disadvantages (Spearman rank correlation)

Question item	Correlation (95%CI) with social disadvantages, p-value		
	Unemployment or unwilling transfer (213/486 cases)	Decrease in income (244/486 cases)	Reduced social positivity (449/486 cases)
1. Insufficient control of symptoms	**0.19 (0.095 – 0.285), <0.0001**	0.08 (−0.01 – 0.18), 0.05	0.05 (−0.04 – 0.14), 0.13
2. Depressive state, changes in mood or character after PSL (PSL use, 81% of subjects)	0.10 (0.00 – 0.19), 0.03	0.02 (−0.08 – 0.12), 0.36	**0.20 (0.10 – 0.28), <0.0001**
3. Changes in appearance after PSL (PSL use, 81% of 486 subjects)	0.07 (−0.03 – 0.16), 0.10	0.05 (−0.05 – 0.15), 0.14	**0.20 (0.11 – 0.28), <0.0001**
4. Diabetes mellitus, osteoporosis, cataracta and/or other arteriosclerotic diseases (PSL use, 81% of subjects)	0.05 (−0.05 – 0.15), 0.16	0.13 (0.03 – 0.22), 0.006	0.12 (0.03 – 0.21), 0.005
5. Side effects related to non-steroid immunosuppressive agents (CNI use, 53%; AZA use, 5%)	−0.02 (−0.12 – 0.07), 0.31	0.05 (−0.05 – 0.15), 0.16	0.08 (−0.01 – 0.17), 0.04
6. Adverse events related to plasmapheresis (28%)	0.04 (−0.06 – 0.14), 0.21	0.07 (−0.03 – 0.17), 0.08	0.04 (−0.05 – 0.13), 0.20
7. Adverse events related to intravenous immunoglobulin (16%)	0.05 (−0.05 – 0.15), 0.17	0.07 (−0.03 – 0.17), 0.08	0.06 (−0.03 – 0.15), 0.08

8. Long-term (>1 month) hospital stay	**0.20 (0.10 – 0.29), <0.0001**	**0.27 (0.19 – 0.37), <0.0001**	−0.05 (−0.14 – 0.04), 0.12
9. Short-term (≤1 week) hospital stay	0.12 (0.02 – 0.24), 0.006	0.13 (0.04 – 0.23), 0.003	0.09 (0.00 – 0.17), 0.03
10. Need to go to the hospital for years	**0.16 (0.07 – 0.26), <0.001**	**0.15 (0.06 – 0.25), <0.001**	0.03 (−0.06 – 0.12), 0.25
11. Need to take various oral drugs for years	0.05 (−0.05 – 0.15), 0.16	0.07 (−0.03 – 0.16), 0.10	0.13 (0.04 – 0.21), 0.002
12. Bias for intractable and uncommon diseases from others	**0.16 (0.06 – 0.26), <0.001**	0.02 (−0.08 – 0.12), 0.35	**0.21 (0.12 – 0.30), <0.0001**

Significant correlations are indicated bold font. AZA, azathioprine; CI, confidence interval; CNI, calcineurin inhibitor; PSL, prednisolone.

Clinical factors from examinations and records

As shown in Table 2, clinical factors were evaluated for each patient and entered into correlation analysis with the social disadvantages. Clinical severity at the worst condition was classified according to MGFA classifications,[17], and in some patients (792/917), was determined according to the quantitative MG score (QMG),[17] from medical records and partly by analyses of information retrospectively. Clinical severity at the current condition was determined according to QMG and the MG Composite (MGC),[18,19] for all patients, who completed the Japanese version of the MG-QOL15 (MG-QOL15-J),[3] at study entry. Clinical status following treatment was categorized according to MGFA postintervention status,[17]. Previously, minimal manifestations (MM) or better status with prednisolone (PSL) at ≤5 mg/day (MM or better-5 mg) was identified as a practical treatment target,[3,4], as the HRQOL of patients with this status was reported to be as good as that of complete stable remission (CSR),[3,4]. This category grouping into MM or better status (i.e., MM, pharmacological remission (PR) or CSR) and a cut-off of the PSL dose at 5 mg/day were proposed according to the results of a previous decision tree analysis for good HRQOL,[3]. The achievement of MM or better-5 mg lasting more than 6 months was determined at 1, 2, and 4 years into treatment from medical records and partly by analyses of information retrospectively, and also determined at study entry. The maximum and current dose of oral PSL and the duration of oral PSL ≥20 mg/day were obtained from the patients' medical records.

Serum AChR-Ab titers were estimated by radioimmunoassay using ^{125}I-α-bungarotoxin, and levels ≥0.5 nM were regarded as positive. MuSK-Ab was measured using a commercially available radioimmunoprecipitation assay (RSR, Cardiff, UK).

The study protocols were approved by the ethics committees of each participating

institution. Written informed consent was obtained from all patients participating in the study.

Table 2. Patient characteristics and associations between clinical factors and social disadvantages (Spearman rank correlation)

Clinical factor	Mean ± standard deviation (range) *(n=917)*	Correlation (95%CI) with social disadvantages, p-value		
		Unemployment or unwilling transfer (213/680 cases)	Decrease in income (244/680 cases)	Reduced social positivity (449/917 cases)
Age, yrs	57.1 ± 15.4 (19–93)	-0.08 (-0.16 – −0.01), 0.02	−0.07 (−0.14 – 0.01), 0.04	0.00 (−0.07 – 0.07), 0.49
Female (%)	65.2 (598/917)	0.11 (0.00 – 0.18), 0.02	0.01 (−0.06 – 0.09), 0.39	**0.17 (0.10 – 0.24), <0.0001**
Time since onset, yrs	11.9 ± 10.7 (0.1–83)	0.08 (0.00 – 0.15), 0.02	-0.01 (−0.08 – 0.07), 0.43	0.00 (−0.07 – 0.08), 0.45
Age at onset, yrs	45.4 ± 18.1 (3–91)	-0.11 (−0.18 – -0.04), 0.0025	-0.04 (−0.12 – 0.03), 0.12	-0.03 (−0.10 – 0.04), 0.22
Thymectomy, %	52.4 (482/917)	**0.18 (0.10 – 0.25), <0.0001**	**0.21 (0.13 – 0.28), <0.0001**	0.12 (0.05 – 0.19), 0.0003
Thymoma, %	25.0 (230/917)	0.01 (−0.09 – 0.10), 0.46	0.05 (−0.05 – 0.15), 0.15	0.01 (−0.08 – 0.11), 0.38
AChR-Ab-positivity, %	81.1 (744/917)	−0.08 (−0.16 – −0.01), 0.02	−0.08 (−0.16 – −0.01), 0.01	-0.05 (−0.12 – 0.02), 0.07
MuSK-Ab-positivity, %	2.5 (23/917)	0.12 (0.00 – 0.23), 0.03	0.07 (−0.05 – 0.18), 0.14	0.09 (−0.03 – 0.20), 0.07
MGFA classification (Worst)	I/II/III/IV/V 208/392/186/37/94	**0.28 (0.21 – 0.35), <0.0001**	**0.31 (0.24 – 0.38), <0.0001**	**0.22 (0.15 – 0.28), <0.0001**
Bulbar symptoms, % (Worst)	49.4 (453/917)	**0.17 (0.10 – 0.25), <0.0001**	**0.18 (0.10 – 0.25), <0.0001**	0.13 (0.06 – 0.20), 0.0002
Worst QMG (n=792)	13.5 ± 7.5 (1–39)	**0.26 (0.18 – 0.33), <0.0001**	**0.32 (0.24 – 0.39), <0.0001**	**0.25 (0.17 – 0.32), <0.0001**
Current QMG	6.6 ± 4.9 (0–29)	**0.20 (0.13 – 0.27), <0.0001**	**0.20 (0.12 – 0.27), <0.0001**	**0.27 (0.20 – 0.34), <0.0001**
Current MGC	4.3 ± 5.2 (0–32)	**0.21 (0.14 – 0.28), <0.0001**	**0.21 (0.13 – 0.28), <0.0001**	**0.28 (0.22 – 0.35), <0.0001**

Current MG-QOL15-J	13.8 ± 13.2 (0–60)	0.35 (0.28 – 0.41), <0.0001	0.34 (0.27 – 0.40), <0.0001	0.48 (0.43 – 0.54), <0.0001
Peak dose of PSL, mg/day	22.0 ± 19.6 (0–80)	**0.16 (0.88 – 0.24), <0.0001**	**0.22 (0.15 – 0.30), <0.0001**	0.08 (0.01 – 0.15), 0.0143
Duration of PSL ≥20 mg/day, yrs	0.72 ± 1.7 (0–19.6)	**0.19 (0.11 – 0.27), <0.0001**	**0.22 (0.14 – 0.30), <0.0001**	**0.15 (0.07 – 0.22), <0.0001**
Current dose of PSL, mg/day	4.4 ± 5.0 (0–40.0)	0.11 (0.03 – 0.19), 0.003	0.12 (0.05 – 0.20), 0.0011	0.11 (0.04 – 0.18), 0.002
MM or better with 5 mg at 1 year into treatment, %	34.0 (299/880)	**-0.17 (−0.24 – −0.09), <0.0001**	**-0.17 (−0.25 – −0.09), <0.0001**	**-0.19 (−0.26 – −0.11), <0.0001**
MM or better with 5 mg at 2 years into treatment, %	40.5 (298/735)	-0.15 (−0.24 – −0.07), 0.0002	-0.12 (-0.21 – -0.04), 0.003	**-0.17 (−0.25 – −0.09), <0.0001**
MM or better with 5 mg at 4 years into treatment, %	46.1 (236/512)	**−0.20 (−0.29 – −0.11), <0.0001**	**-0.17 (−0.26 – −0.08), <0.0001**	**-0.23 (−0.31 – −0.15), <0.0001**
MM or better with 5 mg at present, %	48.9 (448/917)	**−0.17 (−0.24 – −0.10), <0.0001**	**−0.15 (−0.23 – −0.08), <0.0001**	**−0.22 (-0.30 – −0.16), <0.0001**

Significant correlations are indicated bold font. AChR-Ab, antiacetylcholine receptor antibody; CI, confidence interval; MGC, Myasthenia Gravis Composite; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MG-QOL15, 15-item MG-specific quality of life scale; MG-QOL15-J, Japanese version of the MG-QOL15; MM, minimal manifestations; MuSK-Ab, muscle-specific kinase antibody; PSL, prednisolone; QMG, MGFA quantitative MG score.

Statistical analysis

Associations between various clinical parameters and experiences of social disadvantages were evaluated using Spearman rank correlations. Multivariate logistic regression analysis was performed to attempt determining the parameters most significantly associated with social disadvantages. All continuous data are expressed as the mean ± standard deviation and range (min–max). Statistical analyses were performed using UNISTAT version 5.6 (Unistat, London, UK).

RESULTS

Frequency of social disadvantages resulting from MG and its treatment

Among the 917 MG patients who answered our questionnaire survey, 237 responded "not applicable (did not receive income from employment)" for the question items shown in Figure 1, A1–3. After excluding these patients, 185 (27.2%) out of the remaining 680 answered "I have experienced unemployment" (unemployment rate in general population of Japan is 3-4 %, http://www.stat.go.jp/english/index.htm), 28 (4.1%) answered "I have experienced an unwilling job transfer", and 244 (35.9%) answered "I have experienced a decrease in income". Out of 244 who reported experiencing a decrease in income, 115 (47.1%) answered that the decrement in total income was ≥50%.

Among the 917 total patients, 449 (49.0%) answered "My social positivity and activity were reduced", and 486 answered "yes" for at least one of question items in Figure 1, A1–3, and 5. The experiences of unemployment or unwilling job transfer and that of a decrease in income showed significant correlations to the perception of reduced social positivity and activity ($r=0.35$, $p<0.0001$; $r=0.35$, $p<0.0001$) (Spearman rank correlation).

Possible causes perceived by patients and correlations with social disadvantages

Correlations between social disadvantages and the degree (0–3) to which the 486 applicable patients felt each of 12 question items in Figure 1B were possible causes of these disadvantages are shown in Table 1.

The items that exhibited significant positive correlations ($p<0.001$, $r\geq0.15$) to the "experience of unemployment or unwilling job transfer" were: "an insufficient control of MG symptoms"; "long-term (>1 month) hospital stay for treatment"; "need to go to the hospital for years"; and "bias for intractable and uncommon diseases from others". Significant positive correlations with "experience of a decrease in income" were "long-term (>1 month) hospital stay for treatment" and "need to go to hospital for years", and those with "reduced social positivity and activity" were "depressive state, changes in mood or character after oral corticosteroids", "changes in appearance after oral corticosteroids", and "bias for intractable and uncommon diseases from others".

Multivariate logistic regression analysis using the 12 items as variables revealed "an insufficient control of MG symptoms" (odds ratio=1.35, p=0.003); "long-term (>1 month) hospital stay for treatment" (1.26, 0.009); "need to go to the hospital for years" (1.34, 0.023); and "bias for intractable and uncommon diseases from others" (1.32, 0.014) as independent items correlating to "experience of unemployment or unwilling job transfer". Items independently correlating to "experience of a decrease in income" were "diabetes mellitus, osteoporosis, cataracta and/or others" (1.34, 0.044); and "long-term (>1 month) hospital stay for treatment" (1.58, <0.0001), and those correlating to "reduced social positivity and activity" were "changes in appearance after oral corticosteroids" (1.35, 0.026); and "bias for intractable and uncommon diseases from others" (1.51, 0.002) (see Supplementary Table 2).

Clinical parameters and correlations with social disadvantages

The backgrounds of the 917 patients and correlations of clinical parameters with the experience of social disadvantages (in applicable patients) are shown in Table 2.

In 680 patients who received income from employment, the clinical parameters that exhibited significant positive correlations ($p < 0.0001$, $r \geq 0.15$) with "experience of unemployment or unwilling job transfer" and with "experience of a decrease in income" were identical; these were: thymectomy; severity at worst condition (MGFA classification, bulbar symptoms, QMG); severity at current condition (QMG, MGC); peak dose of PSL; and duration of PSL ≥20 mg/day. Conversely, achieving MM or better-5 mg at 1 and 4 years into treatment and at present exhibited significant negative correlations ($p<0.0001$, $r \leq -0.15$).

In the 917 patients, the clinical parameters that exhibited significant positive correlations ($p<0.0001$, $r \geq 0.15$) with "reduced social positivity and activity" were: female sex; severity at worst condition (MGFA classification, QMG); severity at current condition (QMG, MGC); and duration of PSL ≥20 mg/day. Achieving MM or better-5 mg at any time point exhibited a significant negative correlation ($p<0.0001$, $r \leq -0.15$) to this adverse effect.

Multivariate logistic regression analysis using the clinical parameters as variables did not function well and revealed no particular independent parameters correlating to the experience of social disadvantages (see Supplementary Table 3).

In addition, to elucidate which time point of achieving MM or better-5 mg was most significant in inhibiting each of these social disadvantages, multivariate logistic regression analysis was performed using parameters that showed negative correlations as variables. We found that "at 4 years into treatment" was the most significant time point for achieving MM or better-5 mg in regard to inhibiting "experience of unemployment or unwilling job transfer"

(odds ratio 0.61, p=0.03), “experience of a decrease in income” (0.61, 0.04), and “reduced social positivity and activity” (0.49, 0.005).

Current MG-QOL15-J scores correlated positively with each of these social disadvantages (underlined in Table 2), suggesting that the current HRQOL of the patients was worse with such experiences.

DISCUSSION

The questionnaire results demonstrated that unemployment or an unwilling job transfer after MG onset was experienced by 31.3% of the patients, and a decrease in income was experienced by 35.9%, among whom, 47.1% reported a decrease in total income of more than 50%. In a large German MG cohort, 21.0% of the patients experienced hardships in their jobs, and 28.3% were forced to retire early due to MG,[9]. In a study in Thailand, the unemployment rate among MG patients was 26–58%, and reduced income was seen in 43–48%,[10]. In a community-based survey of Australian MG patients, 39.4% had been forced to stop working due to MG, and 19.4% had to change their occupation,[13]. Only 40.6% of that cohort was working at the time of the survey, and the rest were unable to work due to the effects of the disease,[13]. Although the socioeconomic environments of these patients likely differ to some degree, no substantial differences were observed in the frequency of such disadvantages between these countries. Therefore, a substantial number of MG patients are burdened with socioeconomic disadvantages. MG may not be a major public health problem in terms of the number of patients affected; however, in terms of chronic problems due to its lifelong status, MG may have a substantial impact not only on the patients themselves, but also on the community,[9].

The causes of these social disadvantages perceived by the patients themselves

included bias from others, as well as an insufficient control of symptoms and long-term treatment (hospital stay >1 month and visiting the hospital for years). In many instances, the manifestations of MG are much more evident to the patient than to others, and appear to be frequently misunderstood,[20]. Fatigue is a very common symptom in MG, and this can be misinterpreted for laziness in the context of the workplace. Among individuals who have work demands and other responsibilities, such underestimations of MG symptoms interfere with performing social needs,[9,11]. Efforts must be made to help patients with MG achieve early improvement and return to a normal lifestyle as soon as possible,[3,4,6]. Efforts must also be made to better inform the public (particularly employers) about the characteristics of MG symptoms, as fluctuating weakness with fatigability which can be often underestimated at the workplace.

Participation in work is important not only because of financial resources and access to benefits that jobs provide (e.g., health insurance and welfare), but also because of a person's sense of self-respect, social network, and feelings of usefulness and satisfaction,[21,22]. While at work, individuals are stimulated by physical and mental activities,[9]. Job loss is reportedly associated with worse self-perceived HRQOL and increased adverse health behaviors,[22]. In the patients with MG in the present study, experiences of unemployment or unwilling jobs transfers were consistently significantly correlated with the perception of reduced social positivity and low HRQOL scores. Adjustments in the workplace, as well as adequate therapy, are therefore important for patients with MG,[9].

Physical disability is naturally linked to occupational status and the likelihood of losing one's job. However, among the clinical parameters taken from examinations and patient records in the present study, both severity of illness (worst and current status) and dose

of oral steroids (peak dose of PSL and duration of PSL ≥20 mg/day) were positively correlated with "unemployment or an unwilling job transfer" and "a decrease in income". Such associations are consistent with previous reports in which both severity of illness and dose of oral steroids were the most significant factors negatively affecting patients' HRQOL,[3,4]. The severity of the disease tends to affect personal mobility, while the dose of oral steroids tends to affect social mobility,[4]; both of these disadvantages naturally lead to unemployment and a decrease in income.

On the other hand, strangely, thymectomy appeared to positively correlate with both "unemployment or an unwilling job transfer" and "a decrease in income". These unexpected associations were likely due to correlations between thymectomy and other disadvantage-promoting factors such as "long-term (>1 month) hospital stay for treatment" ($r=0.27$, $p<0.0001$)", peak dose of PSL ($r=0.37$, $p<0.0001$), and duration of PSL ≥20 mg/day ($r=0.37$, $p<0.0001$) (Spearman rank correlation). These correlations might have arisen from previous treatment methods in some Japanese institutions in which thymectomy was often followed by high-dose oral steroid therapy utilizing dose escalation and de-escalation. In actuality, performing thymectomy itself is considered to have no direct effect on HRQOL,[10–12] or the social disadvantages of patients with MG.

Achieving MM or better-5 mg likely enables patients to live a normal lifestyle without having to worry about complications resulting from steroids,[3,4], and the achievement of such status negatively correlates with social disadvantages. Interestingly, among 1, 2, and 4 years into treatment and at present, 4 years into treatment appeared to be the most significant time point for inhibiting social disadvantages. The critical time for control of MG is reported to encompass the first several years after onset,[2], and the first 4 years or so into treatment may be a permissible limit to achieve sufficient disease control that leads to a good long-term

condition. Alternatively, for employers, a permissible employment time for patients who have uncontrolled illness and/or are experiencing treatment-related side effects may be limited to the first several years after disease onset. In any case, an early return to a normal lifestyle at least within the first several years of treatment may be important.

Among all patients, 49.0% answered that their "social positivity and activity was reduced", and the self-perceived main causes included "depressive state, changes in mood or character after oral corticosteroids", and "changes in appearance after oral corticosteroids". The most significant clinical factor promoting a depressive state in patients with MG is reportedly an insufficient reduction in the dose of long-term oral steroids,[16]. It is probable that in the patients taking high doses of oral steroids, the problems in appearance and depressive state negatively affect personal relationships, positive thinking, and social activities,[4]. Therefore, for long-term use, oral corticosteroids should be given at the lowest possible dose,[3,4,16,23]. Bias from others and female sex were also associated with decreased social positivity. Therefore, adequate social support, public acceptance, and understanding may be highly beneficial in improving life circumstances among patients with MG,[9,11].

The present study was limited by the facts that a part of clinical factors about subjects was retrospectively obtained, that in some patients, MGFA classifications and postintervention status were re-created by review of clinical data, and that the study was dependent on patients' self-reported data. Whether employment status actually was affected at the time when MG was more severe and patients on more medication could not be addressed. It should be also noted that correlation levels of social disadvantages to the question items and clinical factors for MG were statistically significant but generally low. Naturally, other factors (e.g. careers and experiences of job and educational backgrounds) probably had more

significant effects on social activities and disadvantages, which should be taken into consideration when interpreting the present results.

In conclusion, although this study did have some limitations, among MG patients receiving income from employment in Japan, unemployment or an unwilling job transfer after MG onset was experienced by 31.3%, and a decrease in income by 35.9%, among whom, 47.1% experienced a decrease in total income of more than 50%. Among all patients with MG, 49.0% perceived a reduction in their social positivity. Both severity of illness and the way of treatment affected such disadvantages. An early return to a normal lifestyle without corticosteroid complications (e.g., MM or better-5 mg) is therefore considered a major factor inhibiting such disadvantages. It is also important that employers and coworkers have better informed perceptions about MG, and that patients' workplace or living surroundings help accommodate MG symptoms.

Contributorship statement

Study concept and design: Y Nagane, H Murai, T Imai, N Kawaguchi, M Masuda, M Aoki and K Utsugisawa.

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Drafting the article or revising it critically for important intellectual content: Y Nagane, H Murai, T Imai, D Yamamoto, E Tsuda, N Minami, Y Suzuki, T Kanai, A Uzawa, N Kawaguchi, M Masuda, S Konno, H Suzuki, M Aoki and K Utsugisawa.

Final approval of the version to be published. Y Nagane, H Murai, T Imai, D Yamamoto, E Tsuda, N Minami, Y Suzuki, T Kanai, A Uzawa, N Kawaguchi, M Masuda, S Konno, H Suzuki, M Aoki and K Utsugisawa.

Obtained funding and Study supervision: Y Nagane, H Murai, T Imai, M Aoki and K Utsugisawa.

Competing interests

Dr. Y. Nagane reports no disclosures. Dr. H. Murai reports no disclosures. Dr. T. Imai reports no disclosures. Dr. D. Yamamoto reports no disclosures. Dr. E. Tsuda reports no disclosures. Dr. N. Minami reports no disclosures. Dr. Y. Suzuki reports no disclosures. Dr. T. Kanai reports no disclosures. Dr. A. Uzawa reports no disclosures. Dr. N. Kawaguchi reports no disclosures. Dr. M. Masuda reports no disclosures. Dr. S. Konno reports no disclosures. Dr. H. Suzuki reports no disclosures. Dr. M. Aoki reports no disclosures. Dr. K. Utsugisawa reports no disclosures.

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Data sharing statement

No additional data are available.

REFERENCES

1. Gilhus NE. Autoimmune myasthenia gravis. *Expert Rev Neurother* 2009;9:351–358.
2. Grob D, Brunner N, Namba T, et al. Lifetime course of myasthenia gravis. *Muscle Nerve* 2008;37:141–149.
3. Masuda M, Utsugisawa K, Suzuki S, et al. The MG-QOL15 Japanese version: validation and associations with clinical factors. *Muscle Nerve* 2012;46:166–173.
4. Utsugisawa K, Suzuki S, Nagane Y, et al. Health-related quality-of-life and treatment targets in myasthenia gravis. *Muscle Nerve* 2014;50:493–500.
5. Pascuzzi RM, Coslett HB, Johns TR. Long-term corticosteroid treatment of myasthenia gravis: report of 116 patients. *Ann Neurol* 1984;15:291–298.
6. Sanders DB, Evoli A. Immunosuppressive therapies in myasthenia gravis. *Autoimmunity* 2010;43:428–435.
7. Padua L, Evoli A, Apirile I, et al. Health-related quality of life in patients with myasthenia gravis and the relationship between patient-oriented assessment and conventional measurements. *Neurol Sci* 2001;22:363–369.
8. Paul RH, Nash JM, Cohen RA, et al. Quality of life and well-being of patients with myasthenia gravis. *Muscle Nerve* 2001;24:512–516.
9. Twork S, Wiesmeth S, Klewer J, et al. Quality of life and life circumstances in German myasthenia gravis patients. *Health Qual Life Outcomes* 2010;8:129.
10. Kulkantrakorn K, Sawanyawisuth K, Tiamkao S. Factors correlating quality of life in patients with myasthenia gravis. *Neurol Sci* 2010;31:571–573.
11. Basta IZ, Pekmezović TD, Perić SZ, et al. Assessment of health-related quality of life in patients with myasthenia gravis in Belgrade (Serbia). *Neurol Sci* 2012;33:1375–1381.
12. Boldingh MI, Dekker L, Maniaol AH, et al. An up-date on health-related quality of life in

myasthenia gravis -results from population based cohorts. *Health Qual Life Outcomes* 2015;13:115.

13. Blum S, Lee D, Gillis D, et al. Clinical features and impact of myasthenia gravis disease in Australian patients. *J Clin Neurosci* 2015;22:1164–1169.

14. Burns TM, Conaway MR, Cutter GR, et al. Less is more, or almost as much: a 15-item quality-of-life instrument for myasthenia gravis. *Muscle Nerve* 2008;38:957–963.

15. Burns TM, Grouse CK, Conaway MR, et al.Construct and concurrent validation of the MG-QOL15 in the practice setting. *Muscle Nerve* 2010;41:219–226.

16. Suzuki Y, Utsugisawa K, Suzuki S, et al. Factors associated with depressive state in patients with myasthenia gravis: a multicenter cross-sectional study. *BMJ Open* 2011;1:e000313.

17. Jaretzki A 3rd, Barohn RJ, Ernstoff RM, 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* 2000;55:16–23.

18. Burns TM, Conaway MR, Cutter GR, et al. Construction of an efficient evaluative instrument for myasthenia gravis: the MG composite. *Muscle Nerve* 2008;38:1553–1562.

19. Burns TM, Conaway M, Sanders DB, et al. The MG composite: A valid and reliable outcome measure for myasthenia gravis. *Neurology* 2010;74:1434–1440.

20. Burns TM. History of outcome measures for myasthenia gravis. *Muscle Nerve* 2010;42:5–13.

21. Gignac MA, Lacaille D, Beaton DE, et al. Striking a balance: Work-health-personal life conflict in women and men with arthritis and its association with work outcomes. *J Occup Rehabil* 2014;24: 573–584.

22. van der Hiele K, van Gorp DA, Heerings MA, et al. The MS@Work study: a 3-year

prospective observational study on factors involved with work participation in patients with relapsing-remitting Multiple Sclerosis. *BMC Neurol* 2015;15:134.

23. Nagane Y, Suzuki S, Suzuki N, et al. Early aggressive treatment strategy against myasthenia gravis. *Eur Neurol* 2011;65:16–22.

Questionnaire for investigating the social disadvantages associated with myasthenia gravis and its treatment

JAMG-R ID:

(A) Regarding the social disadvantages resulting from myasthenia gravis (MG) and/or its treatment to date,

1. I have experienced unemployment---------- (1 yes; 0 no; or *not applicable)
2. I have experienced an unwilling job transfer---------- (1 yes; 0 no; or *not applicable)
3. I have experienced a decrease in income---------- (1 yes; 0 no; or *not applicable)
4. If yes, what is the percentage of the decrease in the total income?
------- (1. <10%, 2. 10–25%, 3. 25–50%, 4. ≥50%)
5. I feel as though my social positivity and activity has declined---------- (1 yes; 0 no)

(B) If you answered "yes" to any of the questions above, to what degree is each of the items below (1–12) related to the cause?

Please select the degree of the relationship from the following:

0) Not related at all; 1) May be related; 2) Related to some degree; or 3) Strongly related

1. An insufficient control of MG symptoms----------(0; 1; 2; 3.)
2. Depressive state, or changes in mood or character after oral corticosteroids
----------(0; 1; 2; 3; or *I did not take oral steroids)
3. Changes in appearance after oral corticosteroids---------(0; 1; 2; 3; or *I did not take oral steroids)
4. Side effects of steroids such as diabetes mellitus, osteoporosis, cataracta and/or other arteriosclerotic diseases----------(0; 1; 2; 3; or *I did not take oral steroids)
5. Side effects of non-steroid immunosuppressive agents---(0; 1; 2; 3; or *I did not take such drugs)
6. Adverse events related to plasmapheresis----------(0; 1; 2; 3; or *I did not receive plasmapheresis)
7. Adverse events related to intravenous immunoglobulin-
----------(0; 1; 2; 3; or *I did not receive immunoglobulin)
8. Long-term (>1 month) hospital stay for treatment---------- (0; 1; 2; 3)
9. Short-term (≤1 week) hospital stay for treatment---------- (0; 1; 2; 3)
10. Need to go to the hospital for years---------- (0; 1; 2; 3)
11. Need to take various oral drugs continuously for years---------- (0; 1; 2; 3)
12. Bias for intractable and uncommon diseases from others---------- (0; 1; 2; 3)

Figure 1

184x274mm (300 x 300 DPI)

Supplementary Table 1. Institutions participating in the Japan MG Registry Study 2015

Department of Neurology, Sapporo Medical University Hospital, Sapporo
Department of Neurology, Hokkaido Medical Center, Sapporo
Department of Neurology, Hanamaki General Hospital, Hanamaki
Department of Neurology, Sendai Medical Center, Sendai
Department of Neurology, Tohoku University Graduate School of Medicine, Sendai
Chiba Neurology Clinic, Chiba
Department of Neurology, Chiba University School of Medicine, Chiba
Department of Neurology, Tokyo Medical University, Tokyo
Department of Neurology, Toho University Medical Center Oh-hashi Hospital, Tokyo
Department of Neurology, Tokyo Women's Medical University, Tokyo
Department of Neurology, Kinki University School of Medicine, Osaka
Department of Neurological Therapeutics, Kyushu University Graduate School of Medicine, Fukuoka
Department of Neurology, Nagasaki University Hospital, Nagasaki

MG, myasthenia gravis

Supplementary Table 2. Multivariate logistic regression analysis with question items to social disadvantages

Question item	Odds ratio (95%CI), p-value		
	Unemployment or unwilling transfer (213/486 cases)	Decrease in income (244/486 cases)	Reduced social positivity (449/486 cases)
1. Insufficient control of symptoms	**1.35 (1.11-1.64), 0.0028**	1.08 (0.89-1.32), 0.44	1.12 (0.92-1.36), 0.26
2. Depressive state, changes in mood or character after PSL (PSL use, 81% of subjects)	1.05 (0.81-1.36), 0.72	1.02 (0.78-1.34), 0.86	1.17 (0.86-1.58), 0.32
3. Changes in appearance after PSL (PSL use, 81% of 486 subjects)	0.98 (0.79-1.22), 0.86	0.91 (0.73-1.15), 0.44	**1.35 (1.04-1.75), 0.026**
4. Diabetes mellitus, osteoporosis, cataracta and/or other arteriosclerotic diseases (PSL use, 81% of subjects)	0.97 (0.75-1.26), 0.83	**1.34 (1.01-1.79), 0.044**	1.08 (0.79-1.49), 0.62
5. Side effects related to non-steroid immunosuppressive agents (CNI use, 53%; AZA use, 5%)	0.86 (0.61-1.22), 0.39	1.03 (0.72-1.48), 0.86	1.17 (0.75-1.83), 0.48
6. Adverse events related to plasmapheresis (28%)	0.90 (0.50-1.65), 0.74	0.74 (0.39-1.41), 0.36	1.08 (0.53-2.22), 0.83
7. Adverse events related to intravenous immunoglobulin (16%)	1.14 (0.57-2.28), 0.72	1.95 (0.71-5.36), 0.19	1.37 (0.49-3.84), 0.55
8. Long-term (>1 month) hospital stay	**1.26 (1.06-1.51), 0.0093**	**1.58 (1.30-1.91), <0.0001**	0.79 (0.65-0.95), 0.013
9. Short-term (≤1 week) hospital stay	1.26 (0.90-1.76), 0.17	1.20 (0.83-1.72), 0.33	1.42 (0.97-2.08), 0.07
10. Need to go to the hospital for years	**1.34 (1.04-1.73), 0.023**	1.17 (0.90-1.51), 0.25	0.79 (0.61-1.02), 0.069
11. Need to take various oral drugs for years	0.77 (0.58-1.02), 0.068	0.91 (0.68-1.22), 0.52	1.14 (0.84-1.55), 0.39
12. Bias for intractable and uncommon diseases from others	**1.32 (1.06-1.65), 0.014**	0.89 (0.71-1.11), 0.30	**1.51 (1.16-1.98), 0.0023**

Significant correlations are indicated bold font. AZA, azathioprine; CI, confidence interval; CNI, calcineurin inhibitor; PSL, prednisolone.

Supplementary Table 3. Multivariate logistic regression analysis with clinical factors to social disadvantages

Clinical factor	Odds ratio (95%CI), p-value		
	Unemployment or unwilling transfer (213/680 cases)	Decrease in income (244/680 cases)	Reduced social positivity (449/917 cases)
Age, yrs	6.82 (0.73-64.07), 0.093	0.68 (0.11-4.26), 0.68	0.23 (0.03-1.68), 0.15
Female (%)	0.87 (0.26-2.86), 0.82	0.49 (0.15-1.54), 0.22	1.91 (0.57-6.36), 0.29
Time since onset, yrs	0.14 (0.01-1.36), 0.090	1.40 (0.22-8.98), 0.72	4.48 (0.60-33.72), 0.15
Age at onset, yrs	0.15 (0.02-1.39), 0.094	1.49 (0.23-9.50), 0.67	4.50 (0.60-33.61), 0.14
Thymectomy, %	**16.98 (1.02-282.51), 0.048**	**9.79 (1.10-86.92), 0.041**	0.91 (0.11-7.30), 0.93
Thymoma, %	0.62 (0.15-2.52), 0.51	0.83 (0.22-3.22), 0.79	0.33 (0.08-1.43), 0.14
AChR-Ab-positivity, %	0.28 (0.04-1.79), 0.18	0.27 (0.05-1.42), 0.12	1.26 (0.24-6.60), 0.78
MuSK-Ab-positivity, %	13.13 (0.06-3071.64), 0.35	0.66 (0.02-24.06), 0.82	0.10 (0.00-3.69), 0.21
MGFA classification (Worst)	1.15 (0.62-2.14), 0.65	0.90 (0.51-1.61), 0.73	**2.26 (1.16-4.41), 0.017**
Bulbar symptoms, % (Worst)	0.88 (0.17-4.50), 0.88	1.08 (0.22-5.18), 0.92	0.38 (0.08-1.87), 0.23
Current MGC	1.15 (1.00-1.34), 0.057	1.16 (0.99-1.35), 0.063	1.17 (0.98-1.39), 0.08
Peak dose of PSL, mg/day	1.01 (0.97-1.05), 0.63	1.02 (0.99-1.06), 0.22	0.99 (0.95-1.02), 0.44
Duration of PSL ≥20 mg/day, yrs	1.19 (0.80-1.75), 0.39	1.30 (0.86-1.94), 0.21	0.73 (0.49-1.10), 0.14
Current dose of PSL, mg/day	1.17 (0.99-1.39), 0.062	1.04 (0.92-1.19), 0.53	1.03 (0.91-1.17), 0.64
MM or better with 5 mg at 1 year into treatment, %	0.65 (0.11-3.90), 0.64	1.03 (0.20-5.34), 0.98	0.66 (0.13-3.46), 0.63
MM or better with 5 mg at 2 years into treatment, %	1.49 (0.28-7.98), 0.64	3.72 (0.73-19.02), 0.11	3.17 (0.50-19.92), 0.22
MM or better with 5 mg at 4 years into treatment, %	2.05 (0.37-11.22), 0.41	0.55 (0.12-2.65), 0.46	**0.16 (0.03-0.98), 0.048**
MM or better with 5 mg at present, %	1.29 (0.28-6.00), 0.74	1.72 (0.39-7.52), 0.47	0.73 (0.18-2.93), 0.66

Significant correlations are indicated bold font. AChR-Ab, antiacetylcholine receptor antibody; CI, confidence interval; MGC, Myasthenia Gravis Composite; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MG-QOL15, 15-item MG-specific quality of life scale; MG-QOL15-J, Japanese version of the MG-QOL15; MM, minimal manifestations; MuSK-Ab, muscle-specific kinase antibody; PSL, prednisolone; QMG, MGFA quantitative MG score.

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	Pages 1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 6
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 7-13
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pages 7-13
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 7-13
Bias	9	Describe any efforts to address potential sources of bias	Page 7
Study size	10	Explain how the study size was arrived at	Page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pages 7-13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 14
		(*b*) Describe any methods used to examine subgroups and interactions	Pages 7-14
		(*c*) Explain how missing data were addressed	Page 7
		(*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	Pages 14-16
		(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	Pages 12-13
		(b) Indicate number of participants with missing data for each variable of interest	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	Page 16
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*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	Page 16-19
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 20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 16-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pages 16-17
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 2

*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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Social disadvantages associated with myasthenia gravis and its treatment: A multicenter cross-sectional study

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Social disadvantages associated with myasthenia gravis and its treatment: A multicenter cross-sectional study

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ABSTRACT

Objectives: To clarify the social disadvantages associated with myasthenia gravis (MG) and examine associations with its disease and treatment.

Design: Cross-sectional study.

Setting and Participants: We evaluated 917 consecutive cases of established MG seen at 13 neurological centers in Japan over a short duration.

Outcome measures: All patients completed a questionnaire on social disadvantages resulting from MG and its treatment and a 15-item MG-specific quality of life scale at study entry. Clinical severity at the worst condition was graded according to the MG Foundation of America classification, and that at the current condition was determined according to the quantitative MG score and MG Composite. Maximum dose and duration of dose ≥20mg/day of oral prednisolone during the disease course were obtained from the patients' medical records. Achievement of the treatment target (minimal manifestation status with prednisolone at ≤5 mg/day) was determined at 1, 2, and 4 years after starting treatment and at study entry.

Results: We found that 27.2% of the patients had experienced unemployment, 4.1% had been unwillingly transferred, and 35.9% had experienced a decrease in income, 47.1% of whom reported that the decrease was ≥50% of their previous total income. In addition, 49.0% of the patients reported feeling reduced social positivity. Factors promoting social disadvantages were severity of illness, dose and duration of prednisolone, long-term treatment, and a depressive state and change in appearance after treatment with oral steroids. Early achievement of the treatment target was a major inhibiting factor.

Conclusions: MG patients often experience unemployment, unwilling job transfers, and a decrease in income. In addition, many patients report feeling reduced social positivity. To inhibit the social disadvantages associated with MG and its treatment, a focus needs to be

placed on helping MG patients resume a normal lifestyle as soon as possible by achieving the treatment target.

Strengths and limitations of this study

To avoid inclusion biases, we examined consecutive cases.

We systematically analyzed associations of social disadvantages among a large number of MG patients using detailed clinical parameters.

This study was limited by its cross-sectional and partly retrospective design and the fact that it was dependent on patients' self-reported data.

INTRODUCTION

Myasthenia gravis (MG) is a neuromuscular disease that used to be considered severe and was associated with a high mortality rate; however, because of current treatments, MG has largely become non-lethal,[1,2]. Still, even today, many MG patients find it difficult to maintain their daily activity levels due to insufficient improvement in disease status, and the long-term side effects of treatment with oral corticosteroids,[2–5], because full remission without steroid treatment is rare in MG,[3,4,6]. Health-related quality of life (HRQOL) is reduced in many patients with MG,[3,4,7–13]. Analyses of detailed clinical data have consistently revealed that not only disease severity, but also oral corticosteroid dose, has significant negative effects on self-perceived HRQOL among patients with MG,[3,4]. The oral corticosteroid dose has been shown to affect items of the MG-QOL15, a 15-item MG-specific QOL scale,[14,15], associated with social or community mobility,[4]. It is possible that side effects resulting from treatment with corticosteroids, such as problems associated with appearance or a depressive state, negatively affect personal relationships, positive thinking, and social activities,[4,16].

Many patients with MG cannot fully participate in social activities due to the effects of the disease and its treatment,[4,9–13]. These patients therefore appear to suffer social disadvantages such as unemployment and a decrease in income, which can lead to a lower HRQOL,[9–11,13]. However, information regarding the prevalence of these disadvantages and their detailed associations with MG remains scarce. Therefore, we conducted a cross-sectional questionnaire survey to obtain information on social disadvantages experienced by patients with MG. We also examined possible associations with detailed clinical parameters.

PATIENTS AND METHODS

Patients

This study was conducted at 13 neurological centers (Japan MG Registry Group, see Supplementary Table 1) in Japan. We evaluated patients with established MG between April and July 2015. To avoid potential bias, we enrolled consecutive patients with various disease statuses over a short duration (4 months). During this period, a total of 1088 MG patients visited our hospitals. From this group we were able to collect full detailed clinical data from 923 patients, and 165 were excluded from the study because of insufficient data collection. Data collected included present disease status, past course of MG Foundation of America (MGFA) postintervention status, and current and past treatment regimens. Among these 923 patients, 917 responded completely to a questionnaire we conducted on social disadvantages resulting from MG and its treatment (Fig. 1), provided written informed consent, and underwent analysis.

The diagnosis of MG was based on clinical findings (fluctuating symptoms with easy fatigability and recovery after rest) with amelioration of symptoms after intravenous administration of anticholinesterase, decremental muscle response to a train of low-frequency repetitive nerve stimuli of 3 Hz, or the presence of autoantibodies specific for the acetylcholine receptor (AChR) of skeletal muscle (AChR-Ab) or for muscle-specific tyrosine kinase (MuSK-Ab).

Questionnaire on social disadvantages resulting from MG and its treatment

In the present questionnaire survey (Fig. 1), we first elucidated whether each patient had experienced unemployment, an unwilling job transfer, and/or a decrease in income (Fig. 1A, items 1–3). For the patients who had experienced a decrease in income, we further asked

to what degree their previous total income had decreased (Fig. 1A, item 4). We also asked whether the patients felt that their social positivity and activity had declined due to MG and/or its treatment (Fig. 1A, item 5). Only social disadvantages after disease onset were taken into account.

For the patients who answered "yes" for any of the question items 1–3 or 5 (Fig. 1A), we then asked to what degree (0–3) they thought that each of the 12 items were possible causes of their experienced social disadvantages (Fig. 1B, items 1–12). Correlations between the degree (0–3) of each of the 12 items and each social disadvantage were then calculated (Table 1). This questionnaire was newly developed for this survey.

Table 1. Associations between question items and social disadvantages (Spearman rank correlation)

Question item	Correlation (95%CI) with social disadvantages, p-value		
	Unemployment or unwilling transfer (213/486 cases)	Decrease in income (244/486 cases)	Reduced social positivity (449/486 cases)
1. Insufficient control of symptoms	**0.19 (0.095 – 0.285), <0.0001**	0.08 (−0.01 – 0.18), 0.05	0.05 (−0.04 – 0.14), 0.13
2. Depressive state, changes in mood or character after PSL (PSL use, 81% of subjects)	0.10 (0.00 – 0.19), 0.03	0.02 (−0.08 – 0.12), 0.36	**0.20 (0.10 – 0.28), <0.0001**
3. Changes in appearance after PSL (PSL use, 81% of 486 subjects)	0.07 (−0.03 – 0.16), 0.10	0.05 (−0.05 – 0.15), 0.14	**0.20 (0.11 – 0.28), <0.0001**
4. Diabetes mellitus, osteoporosis, cataracta and/or other arteriosclerotic diseases (PSL use, 81% of subjects)	0.05 (−0.05 – 0.15), 0.16	0.13 (0.03 – 0.22), 0.006	0.12 (0.03 – 0.21), 0.005
5. Side effects related to non-steroid immunosuppressive agents (CNI use, 53%; AZA use, 5%)	−0.02 (−0.12 – 0.07), 0.31	0.05 (−0.05 – 0.15), 0.16	0.08 (−0.01 – 0.17), 0.04
6. Adverse events related to plasmapheresis (28%)	0.04 (−0.06 – 0.14), 0.21	0.07 (−0.03 – 0.17), 0.08	0.04 (−0.05 – 0.13), 0.20
7. Adverse events related to intravenous immunoglobulin (16%)	0.05 (−0.05 – 0.15), 0.17	0.07 (−0.03 – 0.17), 0.08	0.06 (−0.03 – 0.15), 0.08

8. Long-term (>1 month) hospital stay	**0.20 (0.10 – 0.29), <0.0001**	**0.27 (0.19 – 0.37), <0.0001**	−0.05 (−0.14 – 0.04), 0.12
9. Short-term (≤1 week) hospital stay	0.12 (0.02 – 0.24), 0.006	0.13 (0.04 – 0.23), 0.003	0.09 (0.00 – 0.17), 0.03
10. Need to go to the hospital for years	**0.16 (0.07 – 0.26), <0.001**	**0.15 (0.06 – 0.25), <0.001**	0.03 (−0.06 – 0.12), 0.25
11. Need to take various oral drugs for years	0.05 (−0.05 – 0.15), 0.16	0.07 (−0.03 – 0.16), 0.10	0.13 (0.04 – 0.21), 0.002
12. Bias for intractable and uncommon diseases from others	**0.16 (0.06 – 0.26), <0.001**	0.02 (−0.08 – 0.12), 0.35	**0.21 (0.12 – 0.30), <0.0001**

Significant correlations are indicated bold font. AZA, azathioprine; CI, confidence interval; CNI, calcineurin inhibitor; PSL, prednisolone.

Clinical factors from examinations and records

As shown in Table 2, clinical factors were evaluated for each patient and entered into correlation analysis with the social disadvantages. Clinical severity at the worst condition was classified according to MGFA classifications,[17], and in some patients (792/917), was determined according to the quantitative MG score (QMG),[17] from medical records and partly by analyses of information retrospectively. Clinical severity at the current condition was determined according to QMG and the MG Composite (MGC),[18,19] for all patients, who completed the Japanese version of the MG-QOL15 (MG-QOL15-J),[3] at study entry. Clinical status following treatment was categorized according to MGFA postintervention status,[17]. Previously, minimal manifestations (MM) or better status with prednisolone (PSL) at ≤5 mg/day (MM or better-5 mg) was identified as a practical treatment target,[3,4], as the HRQOL of patients with this status was reported to be as good as that of complete stable remission (CSR),[3,4]. This category grouping into MM or better status (i.e., MM, pharmacological remission (PR) or CSR) and a cut-off of the PSL dose at 5 mg/day were proposed according to the results of a previous decision tree analysis for good HRQOL,[3]. The achievement of MM or better-5 mg lasting more than 6 months was determined at 1, 2, and 4 years into treatment from medical records and partly by analyses of information retrospectively, and also determined at study entry. The maximum and current dose of oral PSL and the duration of oral PSL ≥20 mg/day were obtained from the patients' medical records. Serum AChR-Ab titers were estimated by radioimmunoassay using ^{125}I-α-bungarotoxin, and levels ≥0.5 nM were regarded as positive. MuSK-Ab was measured using a commercially available radioimmunoprecipitation assay (RSR, Cardiff, UK).

The study protocols were approved by the ethics committees of each participating institution. Written informed consent was obtained from all patients participating in the study.

Table 2. Patient characteristics and associations between clinical factors and social disadvantages (Spearman rank correlation)

Clinical factor	Mean ± standard deviation (range) *(n=917)*	Correlation (95%CI) with social disadvantages, p-value		
		Unemployment or unwilling transfer (213/680 cases)	Decrease in income (244/680 cases)	Reduced social positivity (449/917 cases)
Age, yrs	57.1 ± 15.4 (19–93)	-0.08 (-0.16 – −0.01), 0.02	−0.07 (−0.14 – 0.01), 0.04	0.00 (−0.07 – 0.07), 0.49
Female (%)	65.2 (598/917)	0.11 (0.00 – 0.18), 0.02	0.01 (−0.06 – 0.09), 0.39	**0.17 (0.10 – 0.24), <0.0001**
Time since onset, yrs	11.9 ± 10.7 (0.1–83)	0.08 (0.00 – 0.15), 0.02	-0.01 (−0.08 – 0.07), 0.43	0.00 (−0.07 – 0.08), 0.45
Age at onset, yrs	45.4 ± 18.1 (3–91)	-0.11 (−0.18 – -0.04), 0.0025	-0.04 (−0.12 – 0.03), 0.12	-0.03 (−0.10 – 0.04), 0.22
Thymectomy, %	52.4 (482/917)	**0.18 (0.10 – 0.25), <0.0001**	**0.21 (0.13 – 0.28), <0.0001**	0.12 (0.05 – 0.19), 0.0003
Thymoma, %	25.0 (230/917)	0.01 (−0.09 – 0.10), 0.46	0.05 (−0.05 – 0.15), 0.15	0.01 (−0.08 – 0.11), 0.38
AChR-Ab-positivity, %	81.1 (744/917)	−0.08 (−0.16 – −0.01), 0.02	−0.08 (−0.16 – −0.01), 0.01	-0.05 (−0.12 – 0.02), 0.07
MuSK-Ab-positivity, %	2.5 (23/917)	0.12 (0.00 – 0.23), 0.03	0.07 (−0.05 – 0.18), 0.14	0.09 (−0.03 – 0.20), 0.07
MGFA classification (Worst)	I/II/III/IV/V 208/392/186/37/94	**0.28 (0.21 – 0.35), <0.0001**	**0.31 (0.24 – 0.38), <0.0001**	**0.22 (0.15 – 0.28), <0.0001**
Bulbar symptoms, % (Worst)	49.4 (453/917)	**0.17 (0.10 – 0.25), <0.0001**	**0.18 (0.10 – 0.25), <0.0001**	0.13 (0.06 – 0.20), 0.0002
Worst QMG (n=792)	13.5 ± 7.5 (1–39)	**0.26 (0.18 – 0.33), <0.0001**	**0.32 (0.24 – 0.39), <0.0001**	**0.25 (0.17 – 0.32), <0.0001**
Current QMG	6.6 ± 4.9 (0–29)	**0.20 (0.13 – 0.27), <0.0001**	**0.20 (0.12 – 0.27), <0.0001**	**0.27 (0.20 – 0.34), <0.0001**
Current MGC	4.3 ± 5.2 (0–32)	**0.21 (0.14 – 0.28), <0.0001**	**0.21 (0.13 – 0.28), <0.0001**	**0.28 (0.22 – 0.35), <0.0001**

Current MG-QOL15-J	13.8 ± 13.2 (0–60)	0.35 (0.28 – 0.41), <0.0001	0.34 (0.27 – 0.40), <0.0001	0.48 (0.43 – 0.54), <0.0001
Peak dose of PSL, mg/day	22.0 ± 19.6 (0–80)	**0.16 (0.88 – 0.24), <0.0001**	**0.22 (0.15 – 0.30), <0.0001**	0.08 (0.01 – 0.15), 0.0143
Duration of PSL ≥20 mg/day, yrs	0.72 ± 1.7 (0–19.6)	**0.19 (0.11 – 0.27), <0.0001**	**0.22 (0.14 – 0.30), <0.0001**	**0.15 (0.07 – 0.22), <0.0001**
Current dose of PSL, mg/day	4.4 ± 5.0 (0–40.0)	0.11 (0.03 – 0.19), 0.003	0.12 (0.05 – 0.20), 0.0011	0.11 (0.04 – 0.18), 0.002
MM or better with 5 mg at 1 year into treatment, %	34.0 (299/880)	**-0.17 (−0.24 – −0.09), <0.0001**	**-0.17 (−0.25 – −0.09), <0.0001**	**-0.19 (−0.26 – −0.11), <0.0001**
MM or better with 5 mg at 2 years into treatment, %	40.5 (298/735)	-0.15 (−0.24 – −0.07), 0.0002	-0.12 (-0.21 – -0.04), 0.003	**-0.17 (−0.25 – −0.09), <0.0001**
MM or better with 5 mg at 4 years into treatment, %	46.1 (236/512)	**−0.20 (−0.29 – −0.11), <0.0001**	**-0.17 (−0.26 – −0.08), <0.0001**	**-0.23 (−0.31 – −0.15), <0.0001**
MM or better with 5 mg at present, %	48.9 (448/917)	**−0.17 (−0.24 – −0.10), <0.0001**	**−0.15 (−0.23 – −0.08), <0.0001**	**−0.22 (-0.30 – −0.16), <0.0001**

Significant correlations are indicated bold font. AChR-Ab, antiacetylcholine receptor antibody; CI, confidence interval; MGC, Myasthenia Gravis Composite; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MG-QOL15, 15-item MG-specific quality of life scale; MG-QOL15-J, Japanese version of the MG-QOL15; MM, minimal manifestations; MuSK-Ab, muscle-specific kinase antibody; PSL, prednisolone; QMG, MGFA quantitative MG score.

Statistical analysis

Associations between various clinical parameters and experiences of social disadvantages were evaluated using Spearman rank correlations. Multivariate logistic regression analysis was performed to attempt determining the parameters most significantly associated with social disadvantages. All continuous data are expressed as the mean ± standard deviation and range (min–max). Statistical analyses were performed using UNISTAT version 5.6 (Unistat, London, UK).

RESULTS

Frequency of social disadvantages resulting from MG and its treatment

Among the 917 MG patients who answered our questionnaire survey, 237 responded "not applicable (did not receive income from employment)" for the question items shown in Figure 1, A1–3. After excluding these patients, 185 (27.2%) out of the remaining 680 answered "I have experienced unemployment" (unemployment rate in general population of Japan is 3-4 %, http://www.stat.go.jp/english/index.htm), 28 (4.1%) answered "I have experienced an unwilling job transfer", and 244 (35.9%) answered "I have experienced a decrease in income". Out of 244 who reported experiencing a decrease in income, 115 (47.1%) answered that the decrement in total income was ≥50%.

Among the 917 total patients, 449 (49.0%) answered "My social positivity and activity were reduced", and 486 answered "yes" for at least one of question items in Figure 1, A1–3, and 5. The experiences of unemployment or unwilling job transfer and that of a decrease in income showed significant correlations to the perception of reduced social positivity and activity ($r=0.35$, $p<0.0001$; $r=0.35$, $p<0.0001$) (Spearman rank correlation).

Possible causes perceived by patients and correlations with social disadvantages

Correlations between social disadvantages and the degree (0–3) to which the 486 applicable patients felt each of 12 question items in Figure 1B were possible causes of these disadvantages are shown in Table 1.

The items that exhibited significant positive correlations ($p<0.001$, $r\geq0.15$) to the "experience of unemployment or unwilling job transfer" were: "an insufficient control of MG symptoms"; "long-term (>1 month) hospital stay for treatment"; "need to go to the hospital for years"; and "bias for intractable and uncommon diseases from others". Significant positive correlations with "experience of a decrease in income" were "long-term (>1 month) hospital stay for treatment" and "need to go to hospital for years", and those with "reduced social positivity and activity" were "depressive state, changes in mood or character after oral corticosteroids", "changes in appearance after oral corticosteroids", and "bias for intractable and uncommon diseases from others".

Multivariate logistic regression analysis using the 12 items as variables revealed "an insufficient control of MG symptoms" (odds ratio=1.35, p=0.003); "long-term (>1 month) hospital stay for treatment" (1.26, 0.009); "need to go to the hospital for years" (1.34, 0.023); and "bias for intractable and uncommon diseases from others" (1.32, 0.014) as independent items correlating to "experience of unemployment or unwilling job transfer". Items independently correlating to "experience of a decrease in income" were "diabetes mellitus, osteoporosis, cataracta and/or others" (1.34, 0.044); and "long-term (>1 month) hospital stay for treatment" (1.58, <0.0001), and those correlating to "reduced social positivity and activity" were "changes in appearance after oral corticosteroids" (1.35, 0.026); and "bias for intractable and uncommon diseases from others" (1.51, 0.002) (see Supplementary Table 2).

Overall, these multivariate regression models picked out similar items to those exhibited univariate correlations with social disadvantages (the last paragraph and Table 1).

Clinical parameters and correlations with social disadvantages

The backgrounds of the 917 patients and correlations of clinical parameters with the experience of social disadvantages (in applicable patients) are shown in Table 2.

In 680 patients who received income from employment, the clinical parameters that exhibited significant positive correlations ($p < 0.0001$, $r \geq 0.15$) with "experience of unemployment or unwilling job transfer" and with "experience of a decrease in income" were identical; these were: thymectomy; severity at worst condition (MGFA classification, bulbar symptoms, QMG); severity at current condition (QMG, MGC); peak dose of PSL; and duration of PSL ≥20 mg/day. Conversely, achieving MM or better-5 mg at 1 and 4 years into treatment and at present exhibited significant negative correlations ($p<0.0001$, $r \leq -0.15$).

In the 917 patients, the clinical parameters that exhibited significant positive correlations ($p<0.0001$, $r \geq 0.15$) with "reduced social positivity and activity" were: female sex; severity at worst condition (MGFA classification, QMG); severity at current condition (QMG, MGC); and duration of PSL ≥20 mg/day. Achieving MM or better-5 mg at any time point exhibited a significant negative correlation ($p<0.0001$, $r \leq -0.15$) to this adverse effect.

Multivariate logistic regression analyses using the clinical parameters as variables did not function well [Goodness of fit: chi-square statistic (Hosmer-Lemeshow test) $p = 0.11$, Cox & Snell's pseudo R-squared =0.28 for "unemployment or unwilling job transfer"; 0.10, 0.18 for "experience of a decrease in income"; and 0.15, 0.26 for "reduced social positivity and activity"] (see Supplementary Table 3). These models failed to pick out most of the parameters that exhibited univariate correlations with social disadvantages (the last paragraph

and Table 2). Thus, we avoided employing the results of multivariate logistic regression models on discussing correlations of particular clinical parameters to the experience of social disadvantages.

In addition, to elucidate which time point of achieving MM or better-5 mg was most significant in inhibiting each of these social disadvantages, multivariate logistic regression analysis was performed using parameters that showed negative correlations as variables. We found that "at 4 years into treatment" was the most significant time point for achieving MM or better-5 mg in regard to inhibiting "experience of unemployment or unwilling job transfer" (odds ratio 0.61, p=0.03), "experience of a decrease in income" (0.61, 0.04), and "reduced social positivity and activity" (0.49, 0.005).

Current MG-QOL15-J scores correlated positively with each of these social disadvantages (underlined in Table 2), suggesting that the current HRQOL of the patients was worse with such experiences.

DISCUSSION

The questionnaire results demonstrated that unemployment or an unwilling job transfer after MG onset was experienced by 31.3% of the patients, and a decrease in income was experienced by 35.9%, among whom, 47.1% reported a decrease in total income of more than 50%. In a large German MG cohort, 21.0% of the patients experienced hardships in their jobs, and 28.3% were forced to retire early due to MG,[9]. In a study in Thailand, the unemployment rate among MG patients was 26–58%, and reduced income was seen in 43–48%,[10]. In a community-based survey of Australian MG patients, 39.4% had been forced to stop working due to MG, and 19.4% had to change their occupation,[13]. Only 40.6% of that cohort was working at the time of the survey, and the rest were unable to work due to the

effects of the disease,[13]. Although the socioeconomic environments of these patients likely differ to some degree, no substantial differences were observed in the frequency of such disadvantages between these countries. Therefore, a substantial number of MG patients are burdened with socioeconomic disadvantages. MG may not be a major public health problem in terms of the number of patients affected; however, in terms of chronic problems due to its lifelong status, MG may have a substantial impact not only on the patients themselves, but also on the community,[9].

The causes of these social disadvantages perceived by the patients themselves included bias from others, as well as an insufficient control of symptoms and long-term treatment (hospital stay >1 month and visiting the hospital for years). In many instances, the manifestations of MG are much more evident to the patient than to others, and appear to be frequently misunderstood,[20]. Fatigue is a very common symptom in MG, and this can be misinterpreted for laziness in the context of the workplace. Among individuals who have work demands and other responsibilities, such underestimations of MG symptoms interfere with performing social needs,[9,11]. Efforts must be made to help patients with MG achieve early improvement and return to a normal lifestyle as soon as possible,[3,4,6]. Efforts must also be made to better inform the public (particularly employers) about the characteristics of MG symptoms, as fluctuating weakness with fatigability which can be often underestimated at the workplace.

Participation in work is important not only because of financial resources and access to benefits that jobs provide (e.g., health insurance and welfare), but also because of a person's sense of self-respect, social network, and feelings of usefulness and satisfaction,[21,22]. While at work, individuals are stimulated by physical and mental activities,[9]. Job loss is reportedly associated with worse self-perceived HRQOL and

increased adverse health behaviors,[22]. In the patients with MG in the present study, experiences of unemployment or unwilling jobs transfers were consistently significantly correlated with the perception of reduced social positivity and low HRQOL scores. Adjustments in the workplace, as well as adequate therapy, are therefore important for patients with MG,[9].

Physical disability is naturally linked to occupational status and the likelihood of losing one's job. However, among the clinical parameters taken from examinations and patient records in the present study, both severity of illness (worst and current status) and dose of oral steroids (peak dose of PSL and duration of PSL ≥20 mg/day) were positively correlated with "unemployment or an unwilling job transfer" and "a decrease in income". Such associations could not be demonstrated in the present multivariate logistic regression probably due to poor model fit, but are consistent with previous reports in which both severity of illness and dose of oral steroids were the most significant factors negatively affecting patients' HRQOL,[3,4]. The severity of the disease tends to affect personal mobility, while the dose of oral steroids tends to affect social mobility,[4]; both of these disadvantages naturally lead to unemployment and a decrease in income.

On the other hand, strangely, thymectomy appeared to positively correlate with both "unemployment or an unwilling job transfer" and "a decrease in income". These unexpected associations were likely due to correlations between thymectomy and other disadvantage-promoting factors such as "long-term (>1 month) hospital stay for treatment" ($r=0.27$, $p<0.0001$)", peak dose of PSL ($r=0.37$, $p<0.0001$), and duration of PSL ≥20 mg/day ($r=0.37$, $p<0.0001$) (Spearman rank correlation). These correlations might have arisen from previous treatment methods in some Japanese institutions in which thymectomy was often followed by high-dose oral steroid therapy utilizing dose escalation and de-escalation. In actuality,

performing thymectomy itself is considered to have no direct effect on HRQOL,[10–12] or the social disadvantages of patients with MG.

Achieving MM or better-5 mg likely enables patients to live a normal lifestyle without having to worry about complications resulting from steroids,[3,4], and the achievement of such status negatively correlates with social disadvantages. Interestingly, among 1, 2, and 4 years into treatment and at present, 4 years into treatment appeared to be the most significant time point for inhibiting social disadvantages. The critical time for control of MG is reported to encompass the first several years after onset,[2], and the first 4 years or so into treatment may be a permissible limit to achieve sufficient disease control that leads to a good long-term condition. Alternatively, for employers, a permissible employment time for patients who have uncontrolled illness and/or are experiencing treatment-related side effects may be limited to the first several years after disease onset. In any case, an early return to a normal lifestyle at least within the first several years of treatment may be important.

Among all patients, 49.0% answered that their “social positivity and activity was reduced”, and the self-perceived main causes included “depressive state, changes in mood or character after oral corticosteroids”, and “changes in appearance after oral corticosteroids”. The most significant clinical factor promoting a depressive state in patients with MG is reportedly an insufficient reduction in the dose of long-term oral steroids,[16]. It is probable that in the patients taking high doses of oral steroids, the problems in appearance and depressive state negatively affect personal relationships, positive thinking, and social activities,[4]. Therefore, for long-term use, oral corticosteroids should be given at the lowest possible dose,[3,4,16,23]. Bias from others and female sex were also associated with decreased social positivity. Therefore, adequate social support, public acceptance, and understanding may be highly beneficial in improving life circumstances among patients with

MG,[9,11].

The present study was limited by the facts that a part of clinical factors about subjects was retrospectively obtained, that in some patients, MGFA classifications and postintervention status were re-created by review of clinical data, and that the study was dependent on patients' self-reported data. Whether employment status actually was affected at the time when MG was more severe and patients on more medication could not be addressed. It should be also noted that correlation levels of social disadvantages to the question items and clinical factors for MG were statistically significant but generally low. Naturally, other factors (e.g. careers and experiences of job and educational backgrounds) probably had more significant effects on social activities and disadvantages, which should be taken into consideration when interpreting the present results.

In conclusion, although this study did have some limitations, among MG patients receiving income from employment in Japan, unemployment or an unwilling job transfer after MG onset was experienced by 31.3%, and a decrease in income by 35.9%, among whom, 47.1% experienced a decrease in total income of more than 50%. Among all patients with MG, 49.0% perceived a reduction in their social positivity. Both severity of illness and the way of treatment affected such disadvantages. An early return to a normal lifestyle without corticosteroid complications (e.g., MM or better-5 mg) is therefore considered a major factor inhibiting such disadvantages. It is also important that employers and coworkers have better informed perceptions about MG, and that patients' workplace or living surroundings help accommodate MG symptoms.

Contributorship statement

Study concept and design: Y Nagane, H Murai, T Imai, N Kawaguchi, M Masuda, M Aoki and K Utsugisawa.

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Drafting the article or revising it critically for important intellectual content: Y Nagane, H Murai, T Imai, D Yamamoto, E Tsuda, N Minami, Y Suzuki, T Kanai, A Uzawa, N Kawaguchi, M Masuda, S Konno, H Suzuki, M Aoki and K Utsugisawa.

Final approval of the version to be published. Y Nagane, H Murai, T Imai, D Yamamoto, E Tsuda, N Minami, Y Suzuki, T Kanai, A Uzawa, N Kawaguchi, M Masuda, S Konno, H Suzuki, M Aoki and K Utsugisawa.

Obtained funding and Study supervision: Y Nagane, H Murai, T Imai, M Aoki and K Utsugisawa.

Competing interests

Dr. Y. Nagane reports no disclosures. Dr. H. Murai reports no disclosures. Dr. T. Imai reports no disclosures. Dr. D. Yamamoto reports no disclosures. Dr. E. Tsuda reports no disclosures. Dr. N. Minami reports no disclosures. Dr. Y. Suzuki reports no disclosures. Dr. T. Kanai reports no disclosures. Dr. A. Uzawa reports no disclosures. Dr. N. Kawaguchi reports no disclosures. Dr. M. Masuda reports no disclosures. Dr. S. Konno reports no disclosures. Dr. H. Suzuki reports no disclosures. Dr. M. Aoki reports no disclosures. Dr. K. Utsugisawa reports no disclosures.

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Data sharing statement

No additional data are available.

REFERENCES

1. Gilhus NE. Autoimmune myasthenia gravis. *Expert Rev Neurother* 2009;9:351–358.
2. Grob D, Brunner N, Namba T, et al. Lifetime course of myasthenia gravis. *Muscle Nerve* 2008;37:141–149.
3. Masuda M, Utsugisawa K, Suzuki S, et al. The MG-QOL15 Japanese version: validation and associations with clinical factors. *Muscle Nerve* 2012;46:166–173.
4. Utsugisawa K, Suzuki S, Nagane Y, et al. Health-related quality-of-life and treatment targets in myasthenia gravis. *Muscle Nerve* 2014;50:493–500.
5. Pascuzzi RM, Coslett HB, Johns TR. Long-term corticosteroid treatment of myasthenia gravis: report of 116 patients. *Ann Neurol* 1984;15:291–298.
6. Sanders DB, Evoli A. Immunosuppressive therapies in myasthenia gravis. *Autoimmunity* 2010;43:428–435.
7. Padua L, Evoli A, Apirile I, et al. Health-related quality of life in patients with myasthenia gravis and the relationship between patient-oriented assessment and conventional measurements. *Neurol Sci* 2001;22:363–369.
8. Paul RH, Nash JM, Cohen RA, et al. Quality of life and well-being of patients with myasthenia gravis. *Muscle Nerve* 2001;24:512–516.
9. Twork S, Wiesmeth S, Klewer J, et al. Quality of life and life circumstances in German myasthenia gravis patients. *Health Qual Life Outcomes* 2010;8:129.
10. Kulkantrakorn K, Sawanyawisuth K, Tiamkao S. Factors correlating quality of life in patients with myasthenia gravis. *Neurol Sci* 2010;31:571–573.
11. Basta IZ, Pekmezović TD, Perić SZ, et al. Assessment of health-related quality of life in patients with myasthenia gravis in Belgrade (Serbia). *Neurol Sci* 2012;33:1375–1381.
12. Boldingh MI, Dekker L, Maniaol AH, et al. An up-date on health-related quality of life in

myasthenia gravis -results from population based cohorts. *Health Qual Life Outcomes* 2015;13:115.

13. Blum S, Lee D, Gillis D, et al. Clinical features and impact of myasthenia gravis disease in Australian patients. *J Clin Neurosci* 2015;22:1164–1169.
14. Burns TM, Conaway MR, Cutter GR, et al. Less is more, or almost as much: a 15-item quality-of-life instrument for myasthenia gravis. *Muscle Nerve* 2008;38:957–963.
15. Burns TM, Grouse CK, Conaway MR, et al.Construct and concurrent validation of the MG-QOL15 in the practice setting. *Muscle Nerve* 2010;41:219–226.
16. Suzuki Y, Utsugisawa K, Suzuki S, et al. Factors associated with depressive state in patients with myasthenia gravis: a multicenter cross-sectional study. *BMJ Open* 2011;1:e000313.
17. Jaretzki A 3rd, Barohn RJ, Ernstoff RM, 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* 2000;55:16–23.
18. Burns TM, Conaway MR, Cutter GR, et al. Construction of an efficient evaluative instrument for myasthenia gravis: the MG composite. *Muscle Nerve* 2008;38:1553–1562.
19. Burns TM, Conaway M, Sanders DB, et al. The MG composite: A valid and reliable outcome measure for myasthenia gravis. *Neurology* 2010;74:1434–1440.
20. Burns TM. History of outcome measures for myasthenia gravis. *Muscle Nerve* 2010;42:5–13.
21. Gignac MA, Lacaille D, Beaton DE, et al. Striking a balance: Work-health-personal life conflict in women and men with arthritis and its association with work outcomes. *J Occup Rehabil* 2014;24: 573–584.
22. van der Hiele K, van Gorp DA, Heerings MA, et al. The MS@Work study: a 3-year

prospective observational study on factors involved with work participation in patients with relapsing-remitting Multiple Sclerosis. *BMC Neurol* 2015;15:134.

23. Nagane Y, Suzuki S, Suzuki N, et al. Early aggressive treatment strategy against myasthenia gravis. *Eur Neurol* 2011;65:16–22.

Figure legends

Figure: Questionnaire on social disadvantages resulting from MG and its treatment

Questionnaire for investigating the social disadvantages associated with myasthenia gravis and its treatment

JAMG-R ID:

(A) Regarding the social disadvantages resulting from myasthenia gravis (MG) and/or its treatment to date,

1. I have experienced unemployment---------- (1 yes; 0 no; or *not applicable)
2. I have experienced an unwilling job transfer---------- (1 yes; 0 no; or *not applicable)
3. I have experienced a decrease in income---------- (1 yes; 0 no; or *not applicable)
4. If yes, what is the percentage of the decrease in the total income?

------- (1. <10%, 2. 10–25%, 3. 25–50%, 4. ≥50%)

5. I feel as though my social positivity and activity has declined---------- (1 yes; 0 no)

(B) If you answered "yes" to any of the questions above, to what degree is each of the items below (1–12) related to the cause?

Please select the degree of the relationship from the following:

0) Not related at all; 1) May be related; 2) Related to some degree; or 3) Strongly related

1. An insufficient control of MG symptoms----------(0; 1; 2; 3.)
2. Depressive state, or changes in mood or character after oral corticosteroids

----------(0; 1; 2; 3; or *I did not take oral steroids)

3. Changes in appearance after oral corticosteroids---------(0; 1; 2; 3; or *I did not take oral steroids)
4. Side effects of steroids such as diabetes mellitus, osteoporosis, cataracta and/or other arteriosclerotic diseases----------(0; 1; 2; 3; or *I did not take oral steroids)
5. Side effects of non-steroid immunosuppressive agents---(0; 1; 2; 3; or *I did not take such drugs)
6. Adverse events related to plasmapheresis----------(0; 1; 2; 3; or *I did not receive plasmapheresis)
7. Adverse events related to intravenous immunoglobulin-

----------(0; 1; 2; 3; or *I did not receive immunoglobulin)

8. Long-term (>1 month) hospital stay for treatment---------- (0; 1; 2; 3)
9. Short-term (≤1 week) hospital stay for treatment---------- (0; 1; 2; 3)
10. Need to go to the hospital for years---------- (0; 1; 2; 3)
11. Need to take various oral drugs continuously for years---------- (0; 1; 2; 3)
12. Bias for intractable and uncommon diseases from others---------- (0; 1; 2; 3)

Figure 1

184x274mm (300 x 300 DPI)

Supplementary Table 1. Institutions participating in the Japan MG Registry Study 2015

Department of Neurology, Sapporo Medical University Hospital, Sapporo
Department of Neurology, Hokkaido Medical Center, Sapporo
Department of Neurology, Hanamaki General Hospital, Hanamaki
Department of Neurology, Sendai Medical Center, Sendai
Department of Neurology, Tohoku University Graduate School of Medicine, Sendai
Chiba Neurology Clinic, Chiba
Department of Neurology, Chiba University School of Medicine, Chiba
Department of Neurology, Tokyo Medical University, Tokyo
Department of Neurology, Toho University Medical Center Oh-hashi Hospital, Tokyo
Department of Neurology, Tokyo Women's Medical University, Tokyo
Department of Neurology, Kinki University School of Medicine, Osaka
Department of Neurological Therapeutics, Kyushu University Graduate School of Medicine, Fukuoka
Department of Neurology, Nagasaki University Hospital, Nagasaki

MG, myasthenia gravis

Supplementary Table 2. Multivariate logistic regression analysis with question items to social disadvantages

Question item	Odds ratio (95%CI), p-value		
	Unemployment or unwilling transfer (213/486 cases)	Decrease in income (244/486 cases)	Reduced social positivity (449/486 cases)
1. Insufficient control of symptoms	**1.35 (1.11-1.64), 0.0028**	1.08 (0.89-1.32), 0.44	1.12 (0.92-1.36), 0.26
2. Depressive state, changes in mood or character after PSL (PSL use, 81% of subjects)	1.05 (0.81-1.36), 0.72	1.02 (0.78-1.34), 0.86	1.17 (0.86-1.58), 0.32
3. Changes in appearance after PSL (PSL use, 81% of 486 subjects)	0.98 (0.79-1.22), 0.86	0.91 (0.73-1.15), 0.44	**1.35 (1.04-1.75), 0.026**
4. Diabetes mellitus, osteoporosis, cataracta and/or other arteriosclerotic diseases (PSL use, 81% of subjects)	0.97 (0.75-1.26), 0.83	**1.34 (1.01-1.79), 0.044**	1.08 (0.79-1.49), 0.62
5. Side effects related to non-steroid immunosuppressive agents (CNI use, 53%; AZA use, 5%)	0.86 (0.61-1.22), 0.39	1.03 (0.72-1.48), 0.86	1.17 (0.75-1.83), 0.48
6. Adverse events related to plasmapheresis (28%)	0.90 (0.50-1.65), 0.74	0.74 (0.39-1.41), 0.36	1.08 (0.53-2.22), 0.83
7. Adverse events related to intravenous immunoglobulin (16%)	1.14 (0.57-2.28), 0.72	1.95 (0.71-5.36), 0.19	1.37 (0.49-3.84), 0.55
8. Long-term (>1 month) hospital stay	**1.26 (1.06-1.51), 0.0093**	**1.58 (1.30-1.91), <0.0001**	0.79 (0.65-0.95), 0.013
9. Short-term (≤1 week) hospital stay	1.26 (0.90-1.76), 0.17	1.20 (0.83-1.72), 0.33	1.42 (0.97-2.08), 0.07
10. Need to go to the hospital for years	**1.34 (1.04-1.73), 0.023**	1.17 (0.90-1.51), 0.25	0.79 (0.61-1.02), 0.069
11. Need to take various oral drugs for years	0.77 (0.58-1.02), 0.068	0.91 (0.68-1.22), 0.52	1.14 (0.84-1.55), 0.39
12. Bias for intractable and uncommon diseases from others	**1.32 (1.06-1.65), 0.014**	0.89 (0.71-1.11), 0.30	**1.51 (1.16-1.98), 0.0023**

Significant correlations are indicated bold font. AZA, azathioprine; CI, confidence interval; CNI, calcineurin inhibitor; PSL, prednisolone.

Supplementary Table 3. Multivariate logistic regression analysis with clinical factors to social disadvantages

Clinical factor	Odds ratio (95%CI), p-value		
	Unemployment or unwilling transfer (213/680 cases)	Decrease in income (244/680 cases)	Reduced social positivity (449/917 cases)
Age, yrs	6.82 (0.73-64.07), 0.093	0.68 (0.11-4.26), 0.68	0.23 (0.03-1.68), 0.15
Female (%)	0.87 (0.26-2.86), 0.82	0.49 (0.15-1.54), 0.22	1.91 (0.57-6.36), 0.29
Time since onset, yrs	0.14 (0.01-1.36), 0.090	1.40 (0.22-8.98), 0.72	4.48 (0.60-33.72), 0.15
Age at onset, yrs	0.15 (0.02-1.39), 0.094	1.49 (0.23-9.50), 0.67	4.50 (0.60-33.61), 0.14
Thymectomy, %	**16.98 (1.02-282.51), 0.048**	**9.79 (1.10-86.92), 0.041**	0.91 (0.11-7.30), 0.93
Thymoma, %	0.62 (0.15-2.52), 0.51	0.83 (0.22-3.22), 0.79	0.33 (0.08-1.43), 0.14
AChR-Ab-positivity, %	0.28 (0.04-1.79), 0.18	0.27 (0.05-1.42), 0.12	1.26 (0.24-6.60), 0.78
MuSK-Ab-positivity, %	13.13 (0.06-3071.64), 0.35	0.66 (0.02-24.06), 0.82	0.10 (0.00-3.69), 0.21
MGFA classification (Worst)	1.15 (0.62-2.14), 0.65	0.90 (0.51-1.61), 0.73	**2.26 (1.16-4.41), 0.017**
Bulbar symptoms, % (Worst)	0.88 (0.17-4.50), 0.88	1.08 (0.22-5.18), 0.92	0.38 (0.08-1.87), 0.23
Current MGC	1.15 (1.00-1.34), 0.057	1.16 (0.99-1.35), 0.063	1.17 (0.98-1.39), 0.08
Peak dose of PSL, mg/day	1.01 (0.97-1.05), 0.63	1.02 (0.99-1.06), 0.22	0.99 (0.95-1.02), 0.44
Duration of PSL ≥20 mg/day, yrs	1.19 (0.80-1.75), 0.39	1.30 (0.86-1.94), 0.21	0.73 (0.49-1.10), 0.14
Current dose of PSL, mg/day	1.17 (0.99-1.39), 0.062	1.04 (0.92-1.19), 0.53	1.03 (0.91-1.17), 0.64
MM or better with 5 mg at 1 year into treatment, %	0.65 (0.11-3.90), 0.64	1.03 (0.20-5.34), 0.98	0.66 (0.13-3.46), 0.63
MM or better with 5 mg at 2 years into treatment, %	1.49 (0.28-7.98), 0.64	3.72 (0.73-19.02), 0.11	3.17 (0.50-19.92), 0.22
MM or better with 5 mg at 4 years into treatment, %	2.05 (0.37-11.22), 0.41	0.55 (0.12-2.65), 0.46	**0.16 (0.03-0.98), 0.048**
MM or better with 5 mg at present, %	1.29 (0.28-6.00), 0.74	1.72 (0.39-7.52), 0.47	0.73 (0.18-2.93), 0.66

Significant correlations are indicated bold font. AChR-Ab, antiacetylcholine receptor antibody; CI, confidence interval; MGC, Myasthenia Gravis Composite; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MG-QOL15, 15-item MG-specific quality of life scale; MG-QOL15-J, Japanese version of the MG-QOL15; MM, minimal manifestations; MuSK-Ab, muscle-specific kinase antibody; PSL, prednisolone; QMG, MGFA quantitative MG score.

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	Pages 1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 6
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 7-13
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pages 7-13
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 7-13
Bias	9	Describe any efforts to address potential sources of bias	Page 7
Study size	10	Explain how the study size was arrived at	Page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pages 7-13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 14
		(*b*) Describe any methods used to examine subgroups and interactions	Pages 7-14
		(*c*) Explain how missing data were addressed	Page 7
		(*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	Pages 14-16
		(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	Pages 12-13
		(b) Indicate number of participants with missing data for each variable of interest	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	Page 16
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*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	Page 16-19
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 20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 16-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pages 16-17
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 2

*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.