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## ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Social disadvantages associated with myasthenia gravis and its treatment: A multicenter cross-sectional study</th>
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<tr>
<td>AUTHORS</td>
<td>Nagane, Yuriko; Murai, Hiroyuki; Imai, Tomihiro; Yamamoto, Daisuke; Tsuda, Emiko; Minami, Naoya; Suzuki, Yasushi; Kanai, Tetsuya; Uzawa, Akiyuki; Kawaguchi, Naoki; Masuda, Masayuki; Konno, Shingo; Suzuki, Hidekazu; Aoki, Masashi; Utsugisawa, Kimiaki</td>
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## VERSION 1 - REVIEW

<table>
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<tr>
<th>REVIEWER</th>
<th>Michael K. Hehir M.D.</th>
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<td></td>
<td>Assistant Professor of Neurosciences</td>
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<td></td>
<td>Chief, Division of Neuromuscular Medicine</td>
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<td></td>
<td>University of Vermont</td>
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<td></td>
<td>United States</td>
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<td>REVIEW RETURNED</td>
<td>04-Aug-2016</td>
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## GENERAL COMMENTS

The authors present an important analysis of the socioeconomic impact of myasthenia gravis in a cohort of patients from multiple clinics in Japan. The results indicate that a large number of patients with MG experience social disadvantage defined as negative outcomes in patient's occupations or decline in social positivity. Many of these negative outcomes are associated with more severe disease status and use of more aggressive immunotherapy. These findings will be of interest to neuromuscular clinicians and may influence future treatment recommendations for patients with MG. I believe the study could be strengthened by addressing the following points.

**Method:**
1. Study enrolled only 923 of 1088 potential subjects. It would be helpful to state why these 165 patients did not participate.
2. Has the survey used in this protocol been validated in other settings or diseases? If so, important to state this in methods section.
3. Patients were recruited to complete the survey at a single clinic visit. Clinical data about disease severity, medications, etc appears to have been collected by chart review. If clinical data was obtained with retrospective analysis should be stated clearly in this section.
4. Is most severe MGFA status and MGFA Post Intervention Status recorded on all patients so could be directly obtained from the charts? If not, how was MGFA and MGFA PIS status determined for each subject (analysis of information from chart review, etc)?

**Results:**
The results section states that both univariate and multivariate analyses were performed. Appears that only univariate included in
tables and text of results section. Did multivariate change any of the associations? Would be helpful to present both sets of data in table format.

Discussion:
Authors could expand on possible limitations of the study. It should be conceded that clinical data about subjects was obtained retrospectively. If MGFA status or PIS were re-created by review of clinical data, may also be a limitation. While PIS MM or better-5mg was strongly associated with better outcomes in the study, retrospective nature and self reported answers do not allow analysis of whether employment status actually was affected at the time when MG was more severe and patients on more medication.

Overall, I think this is an important analysis that will be of interest to readers.

REVIEWER
Carolina Barnett
University Of Toronto. Toronto, Canada

REVIEW RETURNED
08-Aug-2016

GENERAL COMMENTS
This is a cross-sectional study of social disadvantage, defined as self-reported unemployment, reduced wages or perceived disadvantage in MG patients. This is an extremely important topic, considering the chronic nature of MG where the personal and societal costs are often forgotten. The main strengths of this study are the large number of patients from multiple centres, and the structured collection of the main outcomes. I do have some comments regarding some of the methods that I have listed below:

1. On the abstract, the objectives state is to “clarify the social disadvantages associated with myasthenia gravis (MG) and the casual associations with its disease and treatment”. I don’t think that causality can be extrapolated from a cross-sectional study, therefore this should be rephrased.
2. Strengths and limitations: the authors state that “they avoided potential biases”, these biases and how they were avoided should be described in the strengths and limitations statement.
3. In the introduction (line 20) the authors state that MG patients have insufficient HRQOL. I don’t think that thresholds of what “sufficient” or patient acceptable values of HRQOL have been determined for MG patients. This should be reworded to reflect that patients have overall reduced QoL.
4. Regarding the questionnaire used, is this a questionnaire that has been previously validated to study social disadvantage or was developed for this study? This should be clear in the methods. Also, in the results, the percentage of missing answers should be reported, especially for questions 1-3. A high proportion of missing answers can indicate that the patients have difficulties understanding the question and can reduce the validity of the questionnaire.
5. Results: The findings are interesting, however, it should be noted that most correlations, while statistically significant, are low. For example, in table 2, the highest correlation is 0.27, meaning that the variables while correlated to social disadvantage, explain only a small part of the variance, therefore other factors are likely playing a more important role.
6. Table 3 shows the correlations with clinical variables, here the correlations are slightly higher, but still in a low-moderate range, the highest correlation is 0.48. So again, this should be taken into consideration when interpreting the results.

7. It is interesting that the current dose of PDN is not correlated at all with social disadvantage (e.g. unemployment/income), but peak dose of PDN is. Could the peak dose of PDN be correlated with disease status, i.e. more severely affected patients needing higher doses of PDN. Therefore, the peak PDN dose would be a reflection of severity and this is what drives the social disadvantage, rather than the effect of steroids per se? This would explain table 2 findings where the side effects of PDN were not correlated with unemployment or reduced income, but were correlated to self-perceived “social disadvantage”.

8. The authors should provide as supplementary material the results of the multivariable regression models described in the results. If my interpretation is correct, the models were done only using as variables the different MM or better-5mg time points. I suspect that putting these variables in a model would result in high multicollinearity, since they are very likely highly correlated, affecting the interpretation of the models.

9. I think that building a multivariable regression model including the most relevant self-reported and clinical variables would help to elucidate which variables are the most relevant regarding the outcomes studied (unemployment, reduced income, self-perceived social disadvantage). A major strength of this study is the large number of patients. For example, with 213 patients reporting unemployment, a logistic model could fit up to 20 variables and would contribute to a better understanding of this phenomenon.

10. The discussion is well written and brings up very relevant points regarding the burden of MG in terms of employment. I particularly agree with the importance of keeping in mind the frequent underestimation of symptoms and how this can affect patients’ social life and overall QoL.
very interesting to see the spearman rank correlations, however, why not show the results from the univariate analysis and the logistic regression analysis such as written in the methodological section. The sample size should be sufficient to perform logistic regression analysis. Using logistic or linear regression, one could adjust for confounders, such as disease severity and hospitalization, gender, age at diagnosis. In the statistical analysis chapter it is not clear which variable is independent and dependent.

To me it seems that unemployment/ unwilling transfer is clearly correlated to disease severity. Is there more information of when this unemployment / unwilling transfer happened in time in relation to disease start / diagnosis etc. Are these patients able to work, what type of work did they have? How many of them were of older age and likely to stop working anyway? More interesting is whether patients who are able to work, such as those with mild MG or ocular MG, how is the employment rate in this group? How the employment rate is compared to the general population in Japan?

Table 1 could be omitted, or supplemental Table 2 please do use SD, not range too.
A flowchart could be useful

When presenting correlation, it is common to use R2 and β with its confidence interval, not only p-values.

• The Discussion should not reiterate the background or details of results. The focus should be on the impact of the findings on the field, how the results relate to the literature and the strengths and limitations of the design and data.

The conclusion is too long, should be shortened to 1 sentence at the end.

References: there are more references of this topic, among others Raggi Italy, Kaukanionen finland Maniaol Norway

Strobe checklist: I disagree that the number of participants with missing data for each variable is not applicable? Do you know anything about the selection of this patients? About who did not participate? Why not? How is the generalizability of the data for the MG patients in Japan?

Efforts to describe bias could be done more carefully

 VERSION 1 – AUTHOR RESPONSE

For reviewer #1:

Dear Dr. Hehir
Thank you very much for your kind and reasonable comments. I revised our manuscript as much as possible according to your suggestions as below.

Method:
Point 1. ‘It would be helpful to state why these 165 patients did not participate.’
-Response: I agree with you. I rewrote descriptions about patients enrolled as “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.” (page 7, lines 6-8).
Point 2. ‘Has the questionnaire used in this study been validated?’
-Response: This questionnaire was newly developed for this survey and was not validated, which was added in the text (page 8, line 9).

Point 3 and 4. ‘If clinical data was obtained with retrospective analysis should be stated clearly in this section. Is most severe MGFA status and MGFA Post Intervention Status recorded on all patients so could be directly obtained from the charts?’
-Response: I agree with you. I added descriptions such as “…from medical records and partly by analyses of information retrospectively” in the paragraph regarding Clinical factors from examinations and records (page 11, the first and long paragraph).

Results: ‘…Did multivariate change any of the associations? Would be helpful to present both sets of data in table format.’
-Response: In fact, multivariate logistic regression analysis was performed to attempt determining the parameters independently associated with social disadvantages. That functioned well when using 12 question items as variables, and we added summary of the results in the text (page 16, the last paragraph) and the details as Supplementary Table 2. Regrettably, when using many clinical parameters as variables, multivariate logistic regression analysis did not function well and revealed no particular independent parameters, which was commented in the text (page 17, lines 8-6 from bottom), and we added the details as Supplementary Table 3, according to your suggestions.

Discussion: ‘It should be conceded that clinical data about subjects was obtained retrospectively…’
-Response: I agree with you, and I added a paragraph regarding limitations of the study (page 21, the last paragraph), according to the suggestions.

Kimiaki Utsugisawa, MD

For reviewer #2:

Dear Dr. Barnett
Thank you very much for your kind and reasonable comments. I revised our manuscript as much as possible according to your suggestions as below.

Point 1. ‘I don’t think that causality can be extrapolated from a cross-sectional study, therefore this should be rephrased.’
-Response: I agree with you. I rewrote the sentence as “To clarify the social disadvantages associated with myasthenia gravis (MG) and examine associations with its disease and treatment.” (page 3, the first sentence)

Point 2. ‘Strengths and limitations: these biases and how they were avoided should be described in the strengths and limitations statement.’
-Response: I am sorry for our insufficient presentation. I rewrote the sentence as “To avoid inclusion biases, we examined consecutive cases.” (page 5, the first sentence).

Point 3. ‘I don’t think that thresholds of what “sufficient” or patient acceptable values of HRQOL have been determined for MG patients.’
-Response: I rewrote the sentence simply as “Health-related quality of life (HRQOL) is reduced in many patients with MG,[3,4,7–13].” (page 6, lines 7-8), according to your suggestions.
Point 4. ‘Is this a questionnaire that has been previously validated or was developed for this study?’, ‘...the percentage of missing answers should be reported, especially...’
-Response: This questionnaire was newly developed for this survey and was not validated, which was added in the text (page 8, line 9). As among these 923 patients, 917 responded completely to a questionnaire (described in the Patients section, page 7 lines 10-11), there were no missing answers.

Point 5, 6. ‘it should be noted that most correlations, while statistically significant, are low.’, ‘...So again, this should be taken into consideration...’
-Response: I agree with you. I added a paragraph regarding limitations of the study including these issues (page 21, line 3 from bottom to page 22, line 2).

Point 7, 8 and 9. ‘A reflection of severity or the effect of steroids per se?’ ...‘The results of multivariate regression analysis are better to be provided’
-Response: I agree with you, and Dr. Hehir (reviewer #1) gave the same comments as you. In fact, multivariate logistic regression analysis was performed to attempt determining the parameters independently associated with social disadvantages. That functioned well when using 12 question items as variables, and showed “diabetes mellitus, osteoporosis, cataracta and/or others” was one of significant variables. We added summary of the results in the text (page 16, the last paragraph) and the details as Supplementary Table 2. Regrettably, however, when using many clinical parameters as variables, multivariate logistic regression analysis did not function well and revealed no particular independent parameters (and could not distinguish ‘A reflection of severity or the effect of steroids per se?’), which were commented in the text (page 17, lines 8-6 from bottom), and we added the details as Supplementary Table 3, according to your suggestions.

Point 10.
-Response: I appreciate your favorable comments.

Kimiaki Utsugisawa, MD

For reviewer #3:

Dear Dr. Boldingh
Thank you very much for your comments. Partly, it was somewhat difficult for me to catch your suggestions from comments, but I will respond as much as possible to accommodate to your comments as below.

Introduction:
‘Do not reiterate material…. Avoid stating the obvious; our audience consists of neurologists who already have a basic understanding of the topic.’
-Response: I disagree with your comments. Such an article on the sociological domain may be read also by patients, their family, employers and coworkers, and officials concerned with a medical policy.

‘It should contain a concise statement of the problem and your hypothesis,’
-Response: I feel that such ways cannot be applied for all types of study.

Results:
‘avoid repeating numeric data such as statistical test results that are found in the Tables.’
-Response: I think there are not so frequent repetitions of data. And, in some degree, actual data is
better to be included also in the text for a quick reading without checking detailed Tables.

'I think that the authors should use other statistical methods…. The sample size should be sufficient to perform logistic regression analysis…..'
-Response: I agree with you, and Dr. Hehir (reviewer #1) and Dr. Barnett (reviewer #2) gave the same comments. Multivariate logistic regression analysis was performed to attempt determining the parameters independently associated with social disadvantages. That functioned well when using 12 question items as variables, and we added summary of the results in the text (page 16, the last paragraph) and the details as Supplementary Table 2. Regrettably, when using many clinical parameters as variables, multivariate logistic regression analysis did not function well and revealed no particular independent parameters, which was commented in the text (page 17, lines 8-6 from bottom), and we added the details as Supplementary Table 3, according to your suggestions.

'Is there more information of when this unemployment / unwilling transfer happened in time in relation to disease start / diagnosis etc. ‘
-Response: Regrettably, we do not have such detailed data as you commented. To accommodate to your comments, I added a paragraph regarding limitations of the study (page 21, the last paragraph) including such a sentence “Whether employment status actually was affected at the time when MG was more severe and patients on more medication could not be addressed.”.

‘How the employment rate is compared to the general population in Japan?’
-Response: This is a reasonable comment. Unemployment rate in general population of Japan is 3-4 %, which was added in the text (page 15, lines 14-15). Thank you.

'Table 1 could be omitted, or supplemental’
-Response: I agree with you, and moved Table 1 to Supplementary Table 1.

'Table 2 please do use SD, not range too.’
-Response: I do not think so. It is better regarding the present data to show both SD and range for readers.

Discussion:
‘The Discussion should …. on the impact of the findings on the field, how the results relate to the literature and the strengths and limitations of the design and data.’
-Response: I think that such ways probably are right as generalization but cannot be applied for all types of paper. But, I added a paragraph regarding limitations of the study (page 21, the last paragraph), according to the suggestions.

‘The conclusion is too long, should be shortend to 1 sentence at the end.’
-Response: I agree with your comment ‘too long’, and shortened the paragraph. But, I feel there is no need to be 1 sentence.

References:
‘Raggi Italy, Kaukanionen finland, Maniaol Norway’
-Response: I felt the paper by Raggi Italy and that by Maniaol Norway are not much in the proximity to the topic, and regrettably, I could not find that by Kaukanionen Finland in PubMed.

Strobe checklist:
‘I disagree that the number of participants with missing data for each variable is not applicable?…….’
-Response: Please read carefully below (descriptions in the text, page 7 the first paragraph).

“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. …… Among these 923 patients, 917 responded completely to a questionnaire (6 with insufficient response were excluded)."

**VERSION 2 – REVIEW**

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<th>REVIEWER</th>
<th>Carolina Barnett</th>
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<td>University of Toronto, Canada</td>
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<tr>
<td>REVIEW RETURNED</td>
<td>07-Oct-2016</td>
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**GENERAL COMMENTS**

The authors have made several changes according to previous reviews and the manuscript has considerably improved. Specifically, the multivariable regression model adds strengths to the paper. I think that the authors should incorporate the multivariable results more in the discussion, as opposed than just the bivariate correlations. Otherwise, it defeats the purpose of doing a multivariable analysis by dismissing its findings. Please see specific comments below.

1. In the results, the authors state that “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”.

   It is not clear what the authors mean by “did not function well”. It suggests that model fit was poor. If so, they should provide goodness of fit statistics for each model, such as chi square. If what they mean is the lack of association between the outcome and variables in the model, that does not mean that the models are poor it is just a finding. Of note, Supplementary Table 3. (Multivariate logistic regression analysis with clinical factors to social disadvantages) does show that thymectomy was correlated, albeit not strongly, to unemployment and reduced wages. Worst MGFA class was associated with reduced social positivity.

2. In the discussion, authors state that “use 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”. They should add that this correlation was lost when correcting for other confounders.

**VERSION 2 – AUTHOR RESPONSE**

For reviewer #2:

Dear Dr. Barnett

Thank you very much for your kind and reasonable comments and the time you have spent for our paper. I revised our manuscript again according to your suggestions as below.

Specific comment 1:

It is not clear what the authors mean by “did not function well”. It suggests that model fit was poor. If so, they should provide goodness of fit statistics for each model, such as chi square.

-Response: I agree with your reasonable comment, and am sorry for our insufficient presentation. We
added descriptions and rewrote the paragraph as “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.” (Results section, page 16, the last paragraph)

And, in fact, we had attempted to successfully perform multivariate logistic regression analysis also with selected variables by univariate regression, but which had also ended in failure.

Specific comment 2:
In the discussion, authors state that “use of oral steroids (peak dose of PSL and duration of PSL \( \geq 20 \) mg/day) were positively correlated with “unemployment or an unwilling job transfer” and “a decrease in income”. They should add that this correlation was lost when correcting for other confounders.

-Response: We added a description as “Such associations could not be demonstrated in the present multivariate logistic regression probably due to poor model fit, ....” (Discussion section, page 19, lines 11-12) following the sentence mentioned above, according to your suggestion.

General comments:
I think that the authors should incorporate the multivariable results more in the discussion, as opposed than just the bivariate correlations.

-Response: Regarding ‘causes perceived by patients and correlations with social disadvantages’, overall, these multivariate regression models picked out similar items to those exhibited univariate correlations with social disadvantages (page 16, the first sentence). Therefore, I feel that it would be better to avoid duplicating similar discussion. On the other hand, regarding ‘clinical parameters and correlations with social disadvantages’, we avoided employing the results of multivariate logistic regression models due to poor model fit. Given that how did we handle these results were described in the Results section according to your specific comments 1 and 2 as above, I feel that particular discussion on the results of multivariable analyses would not be needed. I would like to ask you to understand the difficulty in addressing to this suggestion in the present analysis. However, the reviewer’s comments are reasonable and should be important in our future study.

**VERSION 3 – REVIEW**

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<td>University of Toronto, Canada</td>
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| REVIEW RETURNED | 20-Jan-2017 |

| GENERAL COMMENTS | The authors have answered all my queries and have made modifications to the paper. I think it has improved considerably and it will be a contribution to the myasthenia research community. |
Social disadvantages associated with myasthenia gravis and its treatment: a multicentre cross-sectional study


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