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Title: Chronic Stress, Depression and Personality Type in Patients with Myasthenia Gravis

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Abstract

Background and purpose: Stress is a known risk factor for the onset and modulation of disease activity in autoimmune disorders. The aim of this cross-sectional study was to determine any associations between myasthenia gravis (MG) severity and chronic stress, depression and personality type.

Methods: We included 179 consecutive adult patients with confirmed MG attending the Neuromuscular Clinic between March 2017 and December 2017. At baseline, patients were assessed clinically and they completed self-administered scales for disease severity, perceived stress, depression and personality type.

Results: Higher disease severity (Myasthenia Gravis Impairment Index) showed a moderate correlation with depression scores (BDI-II, $r=0.52$, $p<0.001$), and a lower correlation with chronic stress (TICS, $r=0.28$, $p=0.001$). Chronic stress scores were different according to personality types (ANOVA $p=0.02$). The linear regression model with MGII score as the dependent variable showed R^2: 0.34, Likelihood ratio chi square: 74.55, with $p<0.0001$. The only variables that predicted disease severity were depression scores ($p<0.0001$) and female sex ($p=0.003$).

Conclusions: We found a significant association of MG severity with depression and chronic stress, as well as with female gender. These findings should raise awareness that the long-term management of MG should address depression and potential stress, and consider behavioural management to prevent stress-related immune imbalance.

Keywords: Myasthenia Gravis, Stress, Depression, Personality.

Running title: MG, stress, depression and personality

INTRODUCTION

Myasthenia gravis (MG) is a rare autoimmune disease with a prevalence of 25.4-27.3/100,000 [1] caused by nicotinic acetylcholine receptor antibodies (AchR) in most patients [2].

The characteristic clinical pattern is of fluctuating weakness [3], so the presentation can overlap with psychiatric disorders. Myasthenic symptoms of fatigue or dyspnea which are also common in psychiatric disorders lead to misdiagnosis of MG. Co-morbid psychiatric symptoms may be misdiagnosed as true myasthenic symptoms [4]. Many patients report mental stress as an important risk factor for the onset and modulation of disease activity in autoimmune disorders [5, 6, 7]. Depression is another confounder for diagnosis and status [14]. The unpredictable progression of MG, risk of crisis, chronic course and medication side-effects reduce quality of life, cause psychological stress and predispose to depression. Psychiatric treatment may aggravate MG [4]. Thus, a clear diagnosis is necessary to optimize therapy.

Contradictory results on emotional factors have been found in MG patients. Depression is frequent [8-14], and those with more severe illnesses have higher levels of psychopathology [7, 14] that also affect quality of life [6, 15]. Others have not found similar results [16-19].

The potential role of the underlying personality profile in MG is unknown although relationships have been observed in other autoimmune disorders [20]. Some personality traits can predict stress level, for example neuroticism is related to increased exposure to stressful life events, negative emotions and frustration [21] and is predictive of long-term health in chronic patients [22]. In contrast, high extraversion and conscientiousness are less affected by daily stresses [21].

The aim of this cross-sectional study was to develop an understanding of the associations between MG severity, depression, chronic stress and personality type. We hypothesized that patients with worse MG disease severity would have higher rates of stress and depression, and that personality traits would correlate with stress, depression and symptoms.

METHODS

Participants:

We offered the study to consecutive MG adult patients attending the Prosserman Family Neuromuscular Clinic, Toronto General Hospital, between March and December 2017. The diagnosis of MG was confirmed by a neuromuscular physician based on the clinical presentation, abnormal single fiber electromyography studies, and positive antibody titres. The University Health Network Research Ethics Board approved the study and all patients provided written informed consent.

Measures:

At baseline, patients completed the Myasthenia Gravis Impairment Index (MGII) for disease severity [23], the short Trier Inventory for Assessment of Chronic Stress (TICS) [24], Beck's Depression Inventory-Second Edition (BDI-II) [25] and the Big 5 Personality Inventory (NEO-PI-Revised) [26]. (See supplementary material for details.)

Statistical Analysis:

Analyses were performed using R, version 3.5.0. Results are presented as counts (N) and proportions (%) or means +/- standard deviations as appropriate. We compared clinical and demographic variables in patients with and without depression (defined by 17 points or more on the BDI-II scale [25]. We also compared patients with low and high levels of stress using a cut-point of 60 points in the TICS-S [24]. Finally, we compared patients with different personality types as defined by NEO-PI-Revised [26]. For continuous variables, the differences between groups were analyzed with t-test or ANOVA (if > 2 groups); we used chi-square tests to compare proportions. We used Pearson correlation coefficients to evaluate the correlation of disease severity with stress level and depression. We built a multivariate linear regression model using the MGII as the dependent variable to find the association between disease severity, level of stress, depression and personality type. We also incorporated relevant demographic and clinical factors (age, sex, thymoma, MG type) in the models; we measured variation inflation factors (VIF) to assess multicollinearity. We also tested interactions for age and sex and used likelihood ratio tests to determine if these interactions were needed. We assessed models with residual plots and compared R^2 statistics, before and after bootstrapping with 100 repetitions. We retained the best fitting model, and reported the estimates and standard error for each variable. P values < 0.05 were considered statistically significant for all analyses.

RESULTS

A total of 179 patients, 52% women, entered the study. Age ranged from 22-86 years, MG duration 1-46 years and MGII 0-55; 82% of patients had generalized disease; 25.7% had thymoma and 55.3% had thymectomy; 126 patients had antibody tests: AchR Ab were found in 62.7% and anti-MuSK antibodies in 4.8%.

In those under 40 years of age (early onset), 75% were female and in late onset the genders were equally distributed (51.3% female, 48.7% male). Men had lower MGII scores compared to women (MGII 11 vs 17, p=0.002). More men had ocular MG (12% vs 24.4%, p=0.03). MGII scores were not associated with presence of thymoma, prior thymectomy or antibody status.

Patients with depression (17.3%) were younger, had earlier age at onset, higher MGII scores and higher stress scores, and were more likely to have generalized disease (Table 1).

Patients with higher levels of stress (11.7%), were younger, with earlier age at onset, higher MGII scores and had more depressive symptoms (Table 2).

Higher disease severity (MGII score) showed a moderate correlation with depression (r=0.52, p<0.0001), and a lower correlation with chronic stress (r=0.28, p=0.0001). Also, there was a moderate positive correlation between stress and depression (r=0.47, p<.0001).

Table 3 shows stress, depression and clinical factors across personality types determined using the Big 5 Personality Inventory [26]. No extroverted patients were found in this cohort. Patients with neuroticism scored higher in MGII, BDI-II and TICS while patients characterized by conscientiousness scored the lowest.

Women were predominant in the agreeableness group (65%) and men in the openness group (62%, p=0.002). Patients characterized by agreeableness and neuroticism were significantly older than those characterized by openness and conscientiousness (62.1±13.1y versus 56.5±14.9y, p=0.01).

Twenty-five patients (14%) reported a subjective association between MG onset and a stressful personal event such as divorce, family member death, work-related stress.

In the linear regression model, with MGII score as the dependent variable, the interaction between sex and age was not significant (p=0.4) and was not included in the final model (supplementary Table 1). Variance inflation factor scores were below 2.5 indicating no multicollinearity. The final model had R^2:0.34, Likelihood ratio chi square: 74.55, with p<0.0001. The only variables that predicted disease severity were depression scores (p<0.0001) and sex (p=0.003), as females had more severe MG.

DISCUSSION

In this cross-sectional study, we found positive correlations between MG severity (MGII score), depression and chronic stress. When adjusting for confounders, only depression scores and female sex were significant predictors of disease severity.

About 5.4% of the Canadian population 15 years or older meet criteria for a mood disorder in the preceding 12 months [27]. Globally, it is estimated that 4.4% of the population have a depressive disorder, and 3.6% an anxiety disorder [28]. Therefore, in our cohort, the 17.3% of MG patients diagnosed with depression was higher than in the general population.

The previously reported rates of depressive symptoms in MG using BDI-II are contradictory ranging from 19 to 40.5% [12 - 14] to no different than in the general population [17, 29]. When mood, evaluative and vegetative subscales for symptoms of depression were compared, prevalence of depression varied from 17 to 41%, suggesting that it can be artificially inflated by the vegetative symptoms of MG [11]. Higher rates of total psychiatric disturbances 51% [7] or anxiety disorders 46.3% [8] in MG patients have been reported. A previous study showed that patients with dysthymia were older with longer disease duration [8]. In our study cohort, patients with depression and higher levels of stress were younger, with an earlier disease onset, all correlated with increased disease severity. These differences might arise from the larger number of patients in our cohort and the use of different scales for depression across the studies.

Previous studies have consistently documented higher rates of depression in women than men at 2:1 [4, 7, 14, 30], but our cohort shows a very slight male predominance in those with depression and higher stress. A potential explanation is that disability affects perceived gender roles. However, although males have more depression that was significantly correlated with disease severity, women were more likely to have greater disease severity. Previous studies have shown similar gender differences in MG severity and quality of life (QoL) with women having worse fatigue and QoL than men [31, 32]. Our study is in keeping with those findings. Overall, QoL in patients with MG has been found to correlate with disease severity [6, 9, 15].

Another study reported that MG onset was associated with physical or emotional stress in 20% of cases, and mental stress triggered exacerbations in up to 60% of MG. They showed that the lower the QoL, the greater the association with depression in MG [6]. In our study, 14% of patients recognized a personal stressful event prior to the onset of the disease. However, this assessment is limited due to the recall bias. Our cohort had patients with lesser disease severity and with lower degrees of stress that was lost in the model, suggesting that depression is the more important predictor with a stronger association with disease severity.

Our data showed higher levels of stress were associated with neuroticism and openness. Patients characterised by conscientiousness had the lowest scores for depression and chronic stress. We did not find a significant correlation between MG severity and personality type.

A study of personality traits and coping styles according to stress level showed that neuroticism, with adjusting covariates of demographic characteristics and the other personality traits, was a risk factor for stress level with odds ratios (OR) OR:1.24 [21]. Increases in conscientiousness and extraversion were found to be associated with improved mental and physical health in another study, whereas increased neuroticism was linked with poorer health [33]. Given that we did not have any patients classified as extroverted and very few with neuroticism, our findings must be considered with caution. In general, women tend to score higher on neuroticism and agreeableness and men often report higher assertiveness and openness to ideas as assessed by the NEO-PI-R [34] as we observed during the study.

A study of 40 female patients with systemic lupus erythematosus, Sjogren's syndrome, vasculitis or polymyositis predominantly showed characteristics of excessive kindness, lack of aggressiveness, self-depreciation and feelings of inferiority and suggested that patients with dysimmune conditions are psychologically fragile and that psychotherapy should be considered in these patients [20]. Another study in 20 lupus female patients found no significant correlation between personality changes and disease activity; however, an important prevalence of depression (65%) was observed [35].

Some limitations of our study are the cross-sectional design, the lack of a compensator healthy control group, absence of some social factors (such as marital status, education), lack of formal psychiatric evaluation, potential confounding of MG symptoms by those in affective disorders, including only stable outpatients with limited disease severity and uncertainty about the temporal association of depression and MG triggers or consequences.

Major strengths are the large number of patients recruited and the stable cohort that avoids overestimation of depression.

In summary, we found a significant association of MG severity with depression and chronic stress, as well as with female gender. These findings should raise awareness that the long-term management of MG should address depression, potential stress and consider behavioural management to prevent stress-related immune imbalance [36]. Personality traits are interconnected with perception of stressful situations and predisposition to depression [21, 37], so the assessment of trigger factors for MG relapse should consider psychological aspects in addition to other common triggers such as infections or medication.

Disclosure of conflicts of interest:

C. Barnett has received consultancy fees from Akcea, Alexion, Grifols And Takeda. She has received research funding from Grifols and Octapharma. None of these are related to this study.

V. Bril has received consultancy fees from UCB, Argenx, Akcea, Alexion, Grifols And Takeda. She has received research funding from Octapharma, UCB, Argenx, Baxalta and Grifols.

A. Bogdan, A. Ali, M. AlQwaifly, A. Abraham, S. Mannan and E. Ng declare no conflicts.

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REFERENCES

1. Breiner A, Widdifield J, Katzberg HD, Barnett C, Bril V, Tu K. Epidemiology of myasthenia gravis in Ontario, Canada. Neuromuscul Disord. 2016 Jan; 26(1): 41-6.
2. Myasthenia gravis foundation of America. James F Howard Jr. Myasthenia gravis – a summary; c2015. Available from: http://www.myasthenia.org/HealthProfessionals/ClinicalOverviewofMG.aspx
3. Evoli A, Batocchi AP, Tonali P. A practical guide to the recognition and management of myasthenia gravis. Drugs1996 Nov; 52:662-70.
4. Kulaksizoglu IB. Mood and anxiety disorders in patients with myasthenia gravis: aetiology, diagnosis and treatment. CNS Drugs. 2007; 21(6):473-81.
5. Malysheva O, Pierer M, Wagner U, Baerwald CG. Stress and rheumatoid arthritis. Z. Rheumatol. 2010 Aug; 69(6):539-43.
6. Blum S, Lee D, Gillis D, McEniery DF, Reddel S, McCombe P. Clinical features and impact of myasthenia gravis disease in Australian patients. J Clin Neurosci. 2015 Jul; 22(7):1164-9.
7. Magni G, Micaglio GF, Lalli R, et al. Psychiatric disturbances associated with myasthenia gravis. Acta Psychiatry. Scand. 1988; 77:443-5.
8. Ybarra MI, Kummer A, Frota ER, Oliveira JT, Gomez RS, Teixeira AL. Psychiatric disorders in myasthenia gravis. Arq Neuropsiquiatr. 2011 Apr; 69(2A):176-9.
9. Braz NFT, Rocha NP, Vieira ELM et al. Muscle strength and psychiatric symptoms influence health-related quality of life in patients with myasthenia gravis. J Clin Neurosci. 2018 Apr; 50:41-44.
10. Hoffmann S, Ramm J, Grittner U, Kohler S, Siedler J, Meisel A. Fatigue in myasthenia gravis: risk factors and impact on quality of life. Brain Behav. 2016 Oct; 6(10):e00538.
11. Paul RH, Cohen RA, Goldstein JM, Gilchrist JM. Severity of mood, self-evaluative, and vegetative symptoms of depression in myasthenia gravis. J Neuropsychiatry Clin Neurosci. 2000; 12:499-501.
12. Alekseeva TM, Gavrilov YV, Kreis OA et al. Fatigue in patients with myasthenia gravis. J Neurol. 2018 Oct; 265(10):2312-21.
13. Fisher J, Parkinson K, Kothari MJ. Self-reported depressive symptoms in myasthenia gravis. Journal of Clinical Neuromuscular Disease. 2003 March; 4(3): 105-8.
14. Aysal F et al. The relationship of symptoms of anxiety and depression with disease severity and treatment modality in myasthenia gravis: a cross-sectional study. Noro Psikiyatr Ars. 2013 Dec; 50(4):295-300.
15. Winter Y, Schepelmann K, Spottke AE, et al. Health related quality of life in ALS, myasthenia gravis and facioscapulohumeral muscular dystrophy. J Neurol. 2010; 257:1473-81.
16. Paradis CM, Friedman S, Lazar RM, Kula RW. Anxiety disorders in a neuromuscular clinic. Am J Psychiatry. 1993 Jul; 150(7):1102-4.
17. Suzuki Y, Utsugisawa K, Suzuki S, et al. Factors associated with depressive state in patients with myasthenia gravis: a multicentre cross-sectional study. BMJ Open 2011 Dec; 1(2):e000313.
18. Doering S, Henze T, Schussler G. Coping with myasthenia gravis and implications for psychotherapy. Arch Neurol. 1993 Jun; 50(6):617-20.
19. Tennant C, Wilby J, Nicholson GA. Psychological correlates of myasthenia gravis: a brief report. J Psychosom Res. 1986; 30(5):575-80.
20. Dupond JL, Humbert P, Taillard C, de Wazieres B, Vuitton D. Relationship between autoimmune diseases and personality traits in women. Presse Med. 1990 Dec 22-29; 19(44):2019-22. French.

21. Afshar H, Roohafza HR, Keshteli AH, Mazaheri M, Feizi A, Adibi P. The association of personality traits and coping styles according to stress level. Journal of Research in Medical Science. 2015 Apr; 20(4): 353-8.
22. Brickman AL, Yount SE, Blaney NT, Rothberg ST, De-Nour AK. Personality traits and long-term health status: The influence of neuroticism and conscientiousness on renal deterioration in Type-1 diabetes. Psychosomatics. 1996; 37(5):459–68.
23. Barnett C, Bril V, Kapral M, Kulkarni AV, Davis A. Myasthenia Gravis Impairment Index. Responsiveness, meaningful change, and relative efficiency. Neurology. 2017 Dec; 89(23): 2357–64.
24. Schulz P, Schlotz W, Becker P. Trierer Inventar zum chronischen Stress (TICS). [Trier inventory for chronic stress (TICS)] Göttingen, Germany: Hogrefe; 2004.
25. Beck, A.T., Steer, R.A., & Brown, G.K. (1996). Manual for the Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation
26. Costa, P. T., & McCrae, R. R. (1992). NEO PI-R professional manual. Odessa, FL: Psychological Assessment Resources. http://www.sjdm.org/dmidi/NEO_PI-R.html.
27. Pearson C, Janz T, Ali J. Mental and substance use disorders in Canada. Health at a Glance. September 2013. Statistics Canada Catalogue no. 82-624-X.
28. World Health Organisation. Depression and Other Common Mental Disorders. Global Health Estimates. 2017. Available from: http://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf;sequence=1
29. Sitek EJ, Bilinska MM, Wieczorek D, Nyka WM. Neuropsychological assessment in myasthenia gravis. Neurol Sci. 2009; 30:9-14.
30. Canadian Psychiatric Association. Canadian clinical practice guidelines for the treatment of depressive disorders. Can J Psychiatry. 2001; 46: Suppl.
31. Tran C, Bril V, Katzberg HD, Barnett C. Fatigue is a relevant outcome in patients with myasthenia gravis. Muscle Nerve. 2018 Aug; 58(2):197-203.
32. Lee I, Kaminski HJ, Xin H, Cutter G. Gender and quality of life in myasthenia gravis patients from the myasthenia gravis foundation of America registry. Muscle Nerve. 2018 Feb 21.
33. Magee CA, Heaven PC, Miller LM. Personality change predicts self-reported mental and physical health. J Pers. 2013 Jun; 81(3):324-34.
34. Costa PT, Terracciano A, McCrae RR. Gender differences in personality traits across cultures: Robust and surprising findings. J Pers Soc Psychol. 2001 Aug; 81(2): 322–31.
35. Ayache DCG; da Costa IP. Personality traits and associated changes in women with lupus. Rev. Bras. Reumatol. 2009 Dec; 49(6):643-657.
36. Stojanovich L, Marisavljevich D. Stress as a trigger of autoimmune disease. Autoimmun Rev. 2008 Jan; 7(3):209-13.
37. van Praag HM. Can stress cause depression? Prog Neuropsychopharmacol Biol Psychiatry. 2004; 28:891–907.

Table 1: Comparison between MG patients with and without depression

Variable	*Patients with depression (BDI-II >16, N=31)*	*Patients without depression (BDI-II <17, N=148)*	*p value*
Age	52.5±14.1	59.8±14.3	**0.01**
Sex M	51.6	47.3	0.66
Disease duration	10.5±9.2	11.5±9.1	0.61
Age at onset	41.9±15.7	48.3±16.2	**0.04**
Thymoma	32.3	24.3	0.36
Thymectomy	71.0	52.0	0.05
Type of MG – G	96.8	79.1	**0.02**
AchR Ab	54.8	41.9	0.19
MuSK	6.5	2.7	0.30
MGII	27.8±15.8	11.1±11.1	**<.0001**
TICS	53.7±18.2	37.9±15.5	**<.0001**

Values are means ± SD or %.

Table 2: Comparison between MG patients with higher and lower stress level

Variable	*Patients with higher level of stress (TICS>60, N=21)*	*Patients with lower level of stress (TICS<61, N=158)*	*p value*
Age	45.7±13.4	60.2±13.8	**<.0001**
Sex M	57.1	46.8	0.37
Disease duration	13±11.4	11.1±8.7	0.36
Age at onset	32.6±14.5	49.1±11.4	**<.0001**
Thymoma	23.8	25.9	0.83
Thymectomy	81.0	52.0	**0.01**
Type of MG – G	90.5	81.0	0.29
AchR Ab	42.9	44.3	0.90
MuSK	9.5	2.5	0.09
MGII	23.7±15.4	12.6±12.9	**0.0005**
BDI-II	17.0±8.4	8.2±7.0	**<.0001**

Values are means ± SD or %.

Table 3: Features of personality types

Personality type	*TICS*	*BDI-II*	*MGII*	*Age*	*Age of onset*	*Sex F/M*	*Thymoma*	*Generalized*
Agreeableness (34%)	37.7	9.5	14.6	62.2	49.6	39/21	26.7%	76.7%
Conscientiousness (29%)	37.6	7.7	12.8	55.9	46.7	28/24	26.9%	86.5%
Neuroticism (2%)	48.2	11.5	21.8	61.8	47.8	2/2	25%	100%
Openness (35%)	45.6	10.3	13.8	56.9	45.3	24/39	27%	82.5%
p value (ANOVA)	**0.02**	0.31	0.62	0.09	0.52	**0.03**	0.96	0.43