Screening for Depression in Myasthenia Gravis

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ABSTRACT

Introduction: There are conflicting reports of depression prevalence in myasthenia gravis (MG), and the influence of somatic symptoms on screening assessments is not clear. We investigated the frequency of somatic and non-somatic symptoms of depression in MG. We also explored the relationship between depression and MG using disease severity and quality of life measures.

Methods*:* Three cohorts of participants (MG, autoimmune disease, and healthy controls) were prospectively assessed with the Beck Depression Inventory 2 (BDI-II) and BDI-Primary Care (BDI-PC) surveys, modified Rankin Scale, MGFA classification, MG-MMT, MG-ADL and MG-QOL15.

Results: A total of 31 MG, 29 disease controls, and 30 healthy controls were enrolled. Depression frequency indicated by BDI-II in MG [48% (15/31)] and disease control [31% (9/29)] was not significantly different [p=0.1968]. However, we found a significantly higher frequency than healthy controls 10% (3/30) [p=0.0016]. In contrast, depression frequency indicated by BDI-PC was similar in the MG 29% (9/31) and disease controls MG, 24% (7/29) [p=0.7737] as well as the healthy controls 10% (3/30) [p=0.1056]. Scores on BDI-II and BDI-PC were strongly correlated (Spearman r=0.8728, p<0.0001).

Using the BDI-II scale, participants with MG who were depressed had higher scores on MG-ADL, and MG-QOL15 than those who were not depressed. The difference in MG-ADL and MG-QOL15 scores remained significant using the BDI-PC score.

Discussion: These findings suggest depression screening assessments that include physical symptoms could overestimate depression in MG and chronic autoimmune neuromuscular disorders. Yet, a higher frequency of self-reported depression is associated with increased disease severity and lower quality of life even when somatic symptoms were excluded (BDI-PC).

Keywords: *Myasthenia gravis, Depression, Beck Depression Inventory-II (BDI-II), Beck Depression Inventory-Primary Care (BDI-PC)*

Introduction

Myasthenia gravis (MG) is a chronic autoimmune disorder characterized by fatigable muscle weakness [1]. MG typically presents with weakness of specific muscle groups including eyelids, extra-ocular muscles, bulbar and limb muscles. Fatigue, tiredness, and lack of energy are common complaints in patients with MG that may be mistaken for depression. Psychological symptoms in MG have been described since 1966 [2]. It has been reported that as many as 20-30% of individuals with MG are initially misdiagnosed with a psychiatric illness [3].

Identification of patients with MG and co-existing depression is important for optimal management. This recognition is particularly important to help avoid unnecessary use of immunosuppressive medications. Several studies have evaluated the prevalence of depression in patients with MG; however, different screening tools were used to establish the diagnosis of depression in each of these studies [4-10]. The various scales used differed in ability to capture and differentiate the affective or mood-related symptoms of depression from physical symptoms of depression. Several scales include questions on fatigue, tiredness, exhaustion, sluggishness, loss of energy and sleep problems, resulting in conflicting conclusions about the prevalence of depression in patients with MG.

Despite some of the studies that reported no increase in depression compared to the general population [6], the majority of the available data support an increased frequency of depression in myasthenia [5, 7, 8, 10, 11]. However, it is unclear if this is independent of somatic symptoms that may be attributable to MG disease activity.

In clinical practice, there is a need for a tool that is valid and easily administered to screen MG patients for the presence of depression. Exhaustive and lengthy psychological tests are unlikely to be performed. Furthermore, understanding whether there is an association between psychiatric symptoms and severity of MG may inform disease management. There are conflicting results regarding whether patients with more severe disease and those treated with immunosuppressive medications are more likely to have mood disorders [12, 13].

The primary aim of this study was to address whether there are differences in the frequency of depression and physical symptoms of depression in patients with MG compared to other chronic autoimmune neuromuscular disorders and healthy controls. We used two screening depression assessments, the Beck Depression Inventory

2 (BDI-II) and Beck Depression Inventory for Primary Care (BDI-PC) self-reported tools. The BDI-PC is a short screening scale independent of physical function that contains a subset of 7 questions from the standard BDI-II, which assess only non-somatic complaints of depression [14]. BDI-PC, also referred to as Beck Depression Inventory—Fast Screen (BDI—FS), is validated against depression diagnosis based on DSM-IV criteria obtained using the Mood Module from the Primary Care Evaluation of Mental Disorders, self-reported depression, and other instruments such as the Patient Health Questionnaire and Neuropsychiatric Inventory. BDI-PC was shown to be reliable and valid in multiple medical illnesses such as end-stage renal disease, pain clinic populations, chronic fatigue syndrome, Parkinson's disease and multiple sclerosis [15-18]. A secondary aim was to explore the relationship between depression and disease severity and quality of life in patients with MG.

Materials and Methods

Study Overview

This was a prospective cross-sectional study performed at The Ohio State University Wexner Medical Center Neuromuscular Clinics. This study was approved by The Ohio State Wexner Medical Center Institutional Review Board, and all participants signed a written consent form. Patients were recruited from the Ohio State University Wexner Medical Center Neuromuscular Clinics. Participants enrolled included adult patients age 18 or older in three different cohorts (MG, disease controls and healthy controls). MG participants were required to have a diagnosis of MG established based on typical clinical picture and positive serological tests and/or decrement on repetitive nerve stimulation or increased jitter on single fiber EMG. Disease control participants had a chronic autoimmune neuromuscular disorder specifically immune-mediated neuropathy or inflammatory myopathy. MG and disease-control participants were recruited from patients seen in the outpatient clinic setting. Individuals with no history of neuromuscular or neurological disease were enrolled as healthy controls. Controls were recruited from the families of potential subjects. Participants were excluded if they were cognitively impaired as judged by the neurologist, unable to provide consent, or had a known psychiatric disorder other than depression.

Participant Assessments

Participant demographics, immunomodulatory treatments, and disease duration were recorded. To assess for the presence of depression, participants completed two screening surveys, the BDI-II and BDI-PC. BDI-II is a self-reported inventory with 21 items, each scored from 0 to 3 [7, 19]. The total score was subdivided to indicate whether the depression was mild (score of 14-19), moderate (score of 20-28) or severe (score of 29—63) [20]. BDI-PC contains a subset of 7 questions from the standard BDI-II, which assess for non-somatic complaints of depression [14]. Items include symptoms of sadness, pessimism, past failure, loss of pleasure, self-dislike, self-criticalness and suicidal thoughts or wishes. BDI-PC score > 4 is considered positive.

We used modified Rankin scores to stratify patients in terms of overall disability.

The modified Rankin score measures the degree of disability and dependence in patients with neurological disorders. Participants with MG were classified using the Myasthenia Gravis Foundation of America (MGFA) classification, and all participants completed manual muscle testing, modified Rankin Scale, MG-Activities of Daily Living (MG-ADL) scale, and MG-Quality of Life (MG-QOL15) scale.

Statistical Analyses

Statistical analyses were performed using Prism version 8.4.2 (Graphpad, San Diego, CA). Descriptive statistics including mean and standard deviation were determined and shown as mean ± standard deviation (SD). Unpaired t-test was for two group comparisons (MG vs Disease controls, MG vs Healthy controls, and Depressed vs Non-depressed MG participants). Frequencies were compared between groups (MG vs Disease controls, MG vs Healthy controls, and Depressed vs Non-depressed MG participants) using Fisher's exact test. Similarly, frequencies of positive screening for depression on the BDI-II and BDI-PC in MG patients, when stratified by sex, were compared using Fisher's exact test. Spearman correlation coefficient was calculated to investigate the relationships between the BDI-II and BDI-PC scores in patients with MG. A p-value <0.05 was considered significant.

Results

A total of 90 participants were enrolled: 31 MG, 29 disease controls, and 30 healthy controls. The study was conducted over a 10-month period. Demographics are detailed in (**Table 1**). MG participants included 17 males and 14 females with a mean age of 56±17 years. MGFA classification at the time of evaluation was as follows: grade 1=8 participants, grade 2=20 participants, and grade 3=3 participants. Average disease duration at the time of evaluation was 10 years, and the majority (93%) of MG participants were on immunosuppressant or immunomodulatory treatment. These included prednisone,

Table 1. Characteristics of enrolled patients.

	MG N=31	Disease-control N=29	MG vs. Disease-control (p value)	Healthy Control N=30	MG vs. Healthy Control (p value)
Age (years± SD)	56±17	51±15	0.2314	42±13	0.0010
Sex (women/men)	17/14	21/8	0.0.0396	22/8	0.0374
Disability (mRS)	1.7±1.1	1.9±1.1	0.4394	0.03±0.18	<0.0001
Disease duration (years ± SD)	10.45±9.7	6.7±8.3	0.1168	0/30 (0%)	
Percentage on immunomodulatory meds	28/31 (93%)	29/29 (100%)	0.2381	0/30 (0%)	
Percentage on prednisone	24/31 (77%)	11/29 (37%)	0.0109	0/30 (0%)	
Percent with depression based on BDI-II scores	15/31 (48%)	9/29 (31%)	0.1968	3/30 (10%)	0.0016
Percent with mild depression based on BDI-II score	6/31 (19%)	6/29 (21%)	>0.9999	3/30 (10%)	04729
Percent with moderate depression based on BDI-II score	6/31 (19%)	2/29 (7%)	0.2566	0/30 (0%)	0.0240
Percent with severe depression based on BDI-II score	3/31 (10%)	1/29 (3%)	0.6128	0/30 (0%)	0.2377
Percent with depression based on BDI-PC score	9/31 (29%)	7/29 (24%)	0.7737	3/30 (10%)	0.1056
Patients on prednisone with depression based on BDI-II score	12/24 (50%)	4/11 (36%)	0.4928		
Patients on prednisone with depression based on BDI-PC score	6/24 (25%)	3/11 (27%)	>0.9999		

azathioprine, mycophenolate, cyclosporine, tacrolimus, intravenous immunoglobulins, and plasmapheresis. The disease controls included 13 patients with inflammatory muscle disease, 11 with CIDP, 4 with multifocal motor neuropathy and 1 with idiopathic neuropathy. All were using an immunosuppressive or immunomodulatory treatment.

There were no significant differences between the MG and disease control participants for age, overall disability using the modified Rankin scale, and disease duration, but there was a higher frequency of women in the disease control group and more patients with MG were on prednisone. Comparing the MG and healthy participants, in the healthy control group there was a higher frequency of women and the participants were younger.

Using the BDI-II scale, depression frequency was similar in MG patients 48% (15/31) and disease control 31% (9/29) but higher than normal controls [p=0.001] (Table 1). In contrast, using the BDI-PC scale, which assesses the affective component of depression, there was no significant difference in MG patient depression frequency compared to disease or healthy controls (**Table 1**). The scores on the BDI-II and BDI-PC showed strong correlation (Spearman r=0.8728, p<0.0001). The majority of MG (80%) and disease control (57%) patients were on prednisone, and at the time of this study, more MG patients were on prednisone as compared with disease controls. When comparing only the MG and disease control patients that were treated with prednisone, the rates of depression in MG were slightly higher, though not significantly, on BDI-II and were similar on BDI-PC.

The scores of the BDI-II defined depression suggests a severity in the moderate to severe range in 60% (9/15) of MG patients, compared to 33% (3/9) of disease controls. Of the MG patients who screened positive for depression using BDI-II, (8/15) 53% were on antidepressant medications at the time of enrollment compared to (3/7) 42% of the disease control. We also explored depression screening when MG patients were stratified by sex to determine the frequencies of depression on the BDI-II and BDI-PC between men and women. On the BDI-II, 6 of 14 (43%) men screened positive for depression and 9 of 17 (53%) of women screened positive for depression (Fisher's exact test, p= 0.7224). On the BDI-PC, 3 of 14 (21%) screened positive for depression and 6 of 17 (35%) of women screened positive for depression (Fisher's exact test, p= 0.4564).

In the MG cohort, clinical characteristics were compared between participants with depression and

Table 2. The differences between depressed and non-depressed patients with myasthenia gravis using the Beck Depression Inventory-II (BDI-II) screening tool.

	MG depressed BDI-II N=15	MG non-depressed BDI-II N=16	p-value
Age (mean ± SD) years	57±12	55±21	0.7086
MG-MMT (range 0-120)	9.6±10.3	4±5.3	0.0608
MG-QOL 15 (range 0-60)	24.3±12.6	12±9.8	0.0046
MG-ADL (range 0-24)	7.5±3.8	4.12±3.3	0.0117
Disease duration (years)	11.9±10.5	9.2±8.6	0.4367
Functional status (mRS)	2.1±0.8	1.1±1.0	0.0042

Table 3. The differences between depressed and non-depressed patients with myasthenia gravis using Beck Depression Inventory-Primary Care (BDI-PC) as screening tool.

	MG depressed BDI-PC N=9	MG non-depressed BDI-PC N=22	p-value
Age (Mean ± SD) years	56±12	56±19	0.9469
MG-MMT (range 0-120)	11.1±12.3	5.3±6.3	0.0953
MG-QOL 15 (range 0-60)	27.6±11.1	15.1±14	0.0095
MG-ADL (range 0-24)	8.5±3.2	4.9±3.7	0.0179
Disease duration (years)	13.2±12.4	9.3±8.4	0.3176
Functional status	2.2±0.8	1.4±1.1	0.0793

Table 4. Comparison of MG patients with depression on BDI-II and BDI-PC versus BDI-PC only

	MG depressed BDI-II and BDI-PC N=9	MG depressed on BDI-PC only N=6	p-value
Age (Mean ± SD) years	56±12	60±14	0.5593
MG-MMT (range 0-120)	10±13	9±8	0.8674
MG-QOL 15 (range 0-60)	27.7±11.1	23.33±12.4	0.4917
MG-ADL (range 0-24)	8.6±3.2	7.2±4.3	0.4854
Disease duration (years)	13.2±12.4	9.5±8.57	0.5361
Functional status	2.2±0.8	2.3±0.8	0.8027

without depression per the BDI-II (**Table 2**) and the BDI-PC (**Table 3**) surveys. When stratified by the BDI-II, age and disease duration were similar in the depressed and non-depressed MG participants, but participants with MG depression had worse scores on MG-ADL, MG-QOL15, and modified Rankin score compared to those who were not depressed (**Table 2**). Also, participants with depression on the BDI-PC showed worse scores for MG-ADL and MG-QOL15, but modified Rankin scores were not significantly different (**Table 3**). Furthermore, we compared clinical characteristics in MG patients with depression on both the BDI-II and BDI-PC versus the group of MG patients with depression on the BDI-PC only which demonstrated no significant differences between the two groups (Table 4).

Discussion

The signs and symptoms of neuromuscular disorders, including MG, may overlap with somatic symptoms of depression. Thus, we hypothesized that such symptoms could be misconstrued as symptoms of depression and could impact depression screening tools. Therefore, we investigated two formats of the BDI, the BDI-II and the BDI-PC.

We found an increased frequency of depression in patients with MG and autoimmune neuromuscular disease controls compared to healthy controls using a BDI-II scale that combines affective and somatic symptoms of depression. In contrast, using the BDI-PC, a tool that exclusively assesses the affective (non-somatic) symptoms of depression, depression frequencies in MG and disease controls, while still higher were not statistically significant.

Most prior studies have suggested that there is an increased frequency of depression in patients with MG as compared with the general population [5, 7, 8, 10, 11].

In our study, we found similar frequencies of depression in participants with MG as compared with other autoimmune neuromuscular disorders. This is aligned with a prior study by Stewart and colleagues [8]. In this study, the frequency of depression in patients with MG was compared to a control group that included mainly non-immune mediated neuromuscular disorders [8]. Our study included control participants with chronic autoimmune neuromuscular diseases requiring the use of immune based therapies. Similar to our study, the study by Stewart et al. showed a lack of difference in physical symptoms between MG and neuromuscular disease control, but comparison to a control group was not performed.

In our study, a higher percent of MG patients were on corticosteroids as compared with the autoimmune control group. There are several reports of increased incidence of mood disorders in the setting of long-term steroids [21, 22]. When comparing frequencies of depression in patients with MG and autoimmune disorders on prednisone, we found no significant differences, but the percentage of patients treated with prednisone and having depression was higher compared with autoimmune controls on BDI-II. Because of the relatively small sample size of patients treated with prednisone in the MG and autoimmune disease controls groups, an effect of steroids cannot be excluded and requires further study.

Over-representation of somatic symptoms in MG and chronic autoimmune neuromuscular disorders is likely captured by BDI-II scale items, such as lack of energy, tiredness and fatigue. Despite that, we noted that almost half of the patients defined as depressed using BDI-II were not on antidepressant medications at enrollment. This underscores the need for increased vigilance in screening for depression in patients with myasthenia and other chronic neuromuscular diseases. There was no evidence that the disease severity by modified Rankin Scale, a measure of overall degree of disability and independence in daily activities, was different between the MG and disease controls.

Our study also demonstrated association between depression and disease severity but not age or disease duration. In patients with depression on the BDI-II, there were more severe findings on measures of disease severity and disease impairment of activities of daily living and quality of life as well as functional status. Interestingly, on the BDI-PC, similar findings were seen for impact on measures of disease severity and disease impairment of activities of daily living and quality of life, but functional status was similar between depressed and non-depressed participants. The findings are complex and difficult to disentangle in regard to cause and effect. It is likely that worse disease severity is associated with worsening depression, but it is also possible that depression could negatively impact disease activity and outcomes. Thus, these findings deserve further attention in future studies. A future study that investigates an interventional treatment for depression in conjunction with disease-specific outcome measures for function and quality of life of MG could provide important insight.

We conclude that BDI-II and BDI-C are easily administered and valid tools suitable for use in the clinical setting to screen for depression in patients with MG. The finding of significantly high frequency of depression in a cohort of patients with predominately mild to moderate disease severity calls for regular screening for depression in patients with MG. Nonetheless, these results must be interpreted with caution given the limitation related to the small sample size and the need for future investigation for convergent validity in this patient population. Larger

prospective trials are needed to address the effect of treatment of depression in MG on overall measures of motor function and quality of life.

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Abbreviations
Myasthenia Gravis (MG)
Beck Depression Inventory 2 (BDI-II)
Beck Depression Inventory - Primary Care (BDI-PC)
Myasthenia Gravis Foundation of America (MGFA)
Myasthenia Gravis Manual Muscle Testing (MG-MMT)
Myasthenia Gravis Activities of Daily Living (MG-ADL)
Myasthenia Gravis Quality of Life-15 (MG-QOL15)

Conflicts of Interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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