Doi: 10.4274/npa.y5611

The Relationship of Symptoms of Anxiety and Depression with Disease Severity and Treatment Modality in Myasthenia Gravis: A Cross-sectional Study

Miyastenia Graviste Anksiyete ve Depresif Belirtilerin, Hastalık Şiddeti ve Tedavi Biçimiyle İlişkisi: Kesitsel Bir Çalışma

Fikret AYSAL[1], Oğuz KARAMUSTAFALIOĞLU[2], Başak ÖZÇELİK[2], Meltem YILMAZ[3], Nesrin KARAMUSTAFALIOĞLU[3], Hüseyin YUMRUKÇAL[2], Onur TANKAYA[4]

[1]Bakırköy Training and Research Hospital for Psychiatry, Neurology and Neurosurgery, Department of Neurology, İstanbul, Turkey
[2]Şişli Etfal Teaching and Research Hospital, Department of Psychiatry, İstanbul, Turkey
[3]Bakırköy Training and Research Hospital for Psychiatry, Neurology and Neurosurgery, Department of Psychiatry, İstanbul, Turkey
[4]Mental Health and Disease Hospital, Psikiaytr Clinic, Samsun, Turkey

ABSTRACT

Introduction: Findings about the relationship between psychopathology and severity of myasthenia gravis (MG) seem scarce and conflicting. The aim of this study was to investigate the relationship of depressive and anxiety symptoms with disease severity and treatment modalities among a cohort of patients with MG.

Methods: Sixty-seven patients, who presented to the neuromuscular outpatient clinic, at a neuropsychiatry hospital in Istanbul, Turkey in a two-month period, were recruited consecutively. A total of 42 patients with MG were invited to participate in the study. None of the patients refused to participate. Severity of MG was assessed according to the Osserman and Genkins classification. The participants were evaluated by a sociodemographic form, the Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Hamilton Depression Rating Scale 17-item version (HAM-D), and the Hamilton Anxiety Rating Scale (HAM-A).

Results: The patients with stage IIB MG had significantly higher scores on the BAI, HAM-D, HAM-A total and somatic anxiety than those with stage I and IIA MG ($p<0.05$). Likewise, the patients taking a combination of prednisolone+pyridostigmine/azathioprine had significantly higher scores on the BAI, HAM-D, HAM-A total and somatic anxiety than those taking only prednisolone ($p<0.05$). Linear regression analysis revealed that disease severity and stressful life events were the factors associated with the HAM-D scores. Disease severity, treatment modalities, and gender were the factors associated with the HAM-A scores.

Conclusion: The results of the present study may suggest that patients with relatively more severe MG or those taking a combination of immunosupressive and anticholinesterase medications need psychiatric/psychological evaluation. *(Archives of Neuropsychiatry 2013; 50: 295-300)*

Key words: Depression, anxiety, myasthenia gravis, stressful life events

Conflict of interest: The authors reported no conflict of interest related to this article.

ÖZET

Amaç: Psikopatolojiyle miyastenia gravis (MG) şiddeti arasındaki ilişkiye dair bulgular az ve çelişkili görünmektedir. Bu çalışmanın amacı, MG hastalarından oluşan küçük bir kohortta, depresyon ve anksiyete ile hastalık şiddeti ve tedavi biçimi arasındaki ilişkiyi anlamaktır.

Yöntem: İki aylık bir süre boyunca, İstanbul'daki bir nöromüsküler hastalıklar polikliniğine ardışık olarak başvuran MG tanısı alan 67 hasta çalışmaya davet edildi ve toplam 42 hasta çalışmaya alındı. Hastaların tümü çalışmaya katılmayı kabul etti. MG şiddeti Osserman ve Genkins sınıflandırmasına göre belirlendi. Katılımcıların durumu, sosyodemografik form, Beck Depresyon Envanteri (BDE), Beck Anksiyete Envanteri (BAE), Hamilton Depresyon Derecelendirme Ölçeği'nin 17 maddeli uyarlaması (HDDÖ) ve Hamilton Anksiyete Derecelendirme Ölçeği (HADÖ) kullanılarak değerlendirildi.

Bulgular: Evre IIB olan MG hastalarının BAE, HDDÖ ile HADÖ toplam ve bedensel anksiyete puanları, evre I ve evre IIA olan MG hastalarının puanlarına göre önemli ölçüde yüksekti ($p<0,05$). Benzer olarak, prednizolon-piridostigmin/azatioprin alan hastaların BAE, HDDÖ ile HADÖ toplam ve bedensel anksiyete puanları, yalnız prednizolon alan hastaların puanlarına göre önemli ölçüde yüksekti ($p<0,05$). Lineer regresyon analizi, hastalık şiddeti ve stresli yaşam olaylarının HDDÖ puanıyla ilişkili etmenler olduğunu ortaya koyuyordu. Hastalık şiddeti, tedavi biçimi ve cinsiyet ise HADÖ puanlarıyla ilişkili etmenlerdi.

Sonuç: Bu çalışmadan, görece şiddetli MG'si olan hastaların veya antikolinesteraz-immunosupresif kombinasyonu kullanan hastaların psikiyatrik/psikolojik açıdan dikkatle değerlendirilmelerinin gerekebileceği sonucu çıkarılabilir. *(Nöropsikiyatri Arşivi 2013; 50: 295-300)*

Anahtar kelimeler: Depresyon, anksiyete, miyastenia gravis, stresli yaşam olayı

Çıkar çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Correspondence Address/Yazışma Adresi
Fikret Aysal MD, Bakırköy Neuropsychiatry Teaching and Research Hospital, Department of Neurology, İstanbul, Turkey
Gsm: +90 505 450 98 53 E-mail: fikretaysal@yahoo.com **Received/Geliş tarihi:** 13.04.2010 **Accepted/ Kabul tarihi:** 14.08.2012

Introduction

Neurological disorders may present with symptoms of affection, cognition, and behavior. Craig (1) reported that consultation requests from neurology clinics have a prevalence of 12%. Mood disorders are the most common comorbidities in neurological disorders (2). It has been observed that requests from consultation-liaison psychiatry for patients with neuroimmunological disases are relatively rare. In the literature, the data on the relationship of psychiatric disorders with myasthenia gravis (MG), Guillan-Barré syndrome, and multiple sclerosis seem inadequate (3,4).

MG, which has not been defined as a specific illness until the late 19th century, is an autoimmune, life-long and remitting/relapsing disease with an unpredictable course causing disability. MG has a prevalence of 6/100000 (4). Nicotinic acetyhlcoline receptor antibodies block the neuromuscular junction leading to muscle weakness in MG.

Depression has been documented to be under-treated and under-recognized since the obscure and mild symptoms of medical diseases may overlap with the somatic symptoms of depression (2,5,7,8). Only three studies focused on Axis I comorbidities of MG; and the most common comorbidities found were mood and anxiety disorders (6,9,10). The patients with more severe illnesses were reported to have higher levels of psychopathology than those with relatively less severe forms of the illness (6). On the other hand, Paradis (1993) (9) reported no association between the severity of MG and psychopathology. Findings on the relationship between the severity of MG and psychopathology seem inadequate and conflicting (11). The present study aimed to investigate the relationship of depression and anxiety with severity of the illness and the treatment modalities among a small cohort of patients with MG.

Method

Participants

Sixty-seven patients seen consecutively in Istanbul Bakirkoy Neuropsychiatry Teaching and Research Hospital Neuromuscular Diseases Outpatient Clinic for a two-month period were invited to participate in the study. The diagnosis of MG was confirmed by F. A. via clinical and electrophysiological findings and/or the presence of anti-acetylcholine receptor antibodies in serum. All patients underwent thoracic computed tomography (CT); thymectomy was performed when indicated, and histopathological examinations were performed. The participants were evaluated by a psychiatrist using a semi-structured interview. In this interview, the participants were assessed for the presence of alcohol/substance abuse, mental retardation, dementia, schizophrenia, schizoaffective disorder and bipolar disorder. 15 patients with a neurological disease other than MG, or with a chronic illness, or with the above-mentioned psychiatric disorders, or who were illiterate were excluded. 7 patients with a history of psychiatric treatment or any psychotropic use in the past three months, and 3 patients with significant bulbar symptoms or respiratory distress were also excluded. 42 patients meeting the inclusion criteria were invited to participate in the study and all the patients accepted. Severity of MG was evaluated by the Osserman and Genkins Classification (stage I: ocular; stage IIA: mildly generalized, no crisis; stage IIB: moderately generalized, inadequate treatment response, bulbar involvement, no crisis; stage III: acute fulminant myasthenia, profound symptoms with respiratory crisis, no response to treatment, high mortality; stage IV: late and profound myasthenia with same findings as stage III) (12). The study protocol was approved by the instutional review board (IRB). All participants signed a written consent form.

Measurements

Sociodemographic questionnaire: A questionnaire recording information on age, marital status, educational status, information about the illness, diagnosis time and duration of illness was generated for the study.

Each participant was evaluated by a competent psychiatrist using 4 different scales with regard to depressivity and anxiety level. These scales were the Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Hamilton Depression Rating Scale-17 items (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A). Patients with a score above the cut-off were referred to the psychiatric outpatient clinic.

Beck Depression Inventory (BDI) is a commonly used inventory to detect and to follow-up the symptoms of depression. The BDI consists of 21 items all of which evaluate the severity of the

Table 1. Sociodemographic characteristics and illness-related data of the participants with MG

	N	%
Gender		
female	31	74
male	11	26
Marital status		
married	30	71
single	8	19
divorced/widow	4	10
Educational status		
≤ 5-year	6	14
5-8-year	27	64
9-11-year	9	22
MG duration		
1 year	4	10
1-3 years	14	33
> 3 years	24	57
Diagnosis time		
< 1 year	30	71
≥ 1 year	12	29
Osserman and Genkins Classification*		
Stage I	6	14
Stage IIA	29	69
Stage IIB	7	17
Treatment		
Prednisolone	23	55
Combination $	19	45

* Osserman and Genkins classification; stageI: ocular; stage IIA: mildly generalized, no crisis; stageIIB: moderately generalized, inadequate treatment response, bulbar involvement, no crisis.
$prednisolone and azathioprine or pyridostigmine
MG: Myasthenia Gravis.

symptoms from 0 to 3 on a Likert-like scale; total score is between 0 and 63. Higher scores indicate higher levels of depression (13). The Turkish reliability and validity study was performed by Hisli et al. (14). The cut-off score for depression is 16.

Beck Anxiety Inventory (BAI) is a self-rating inventory consisting of 21 items each defining an anxiety symptom. The BAI is recommended for the evaluation of anxiety. Each item evaluates the symptom on a Likert-like scale ranging from 0 to 3. Total score is between 0 and 63. The cut-off score for anxiety is 29. Higher scores indicate higher levels of anxiety (15).The Turkish reliability and validity study was performed by Ulusoy et al. (16).

Hamilton Depression Rating Scale-17 items (HAM-D) is the most commonly used clinician-rated scale for the evaluation of depression. The HAM-D consists of 17 items with a maximum score of 53. Higher scores indicate higher levels of depressive symptoms (17). The cut-off score for depression has been reported to be 18 in the reliability and validity study by Akdemir et al. (18).

Hamilton Anxiety Rating Scale (HAM-A) measures the severity of anxiety symptoms. The HAM-A is a clinician-rated scale consisting of 14 items. Each item comprises a series of symptoms and the HAM-A evaluates both psychic and somatic anxiety (19). Total score range from 0 to 56. Higher scores indicate higher levels of anxiety. The Turkish reliability and validity study was performed by Yazici et al. (20). However, no cut-off score for anxiety was computed.

Stressful Life Events were evaluated by the question "Have you experienced a stressful or negatively effecting life-event in the past six months? If so, please explain". Financial, relationship-related (separation, divorce, break up), occupational, academic and legal issues, disease, death of a close friend or a relative, and accommodation problems were all accepted as stressful life events. However, onset or progression of MG was not admitted as a stressful life event for the study.

Statistical Analysis

Data transfer and analysis were performed using SPSS 13.0 for Windows. The distrubition of nominal values were not normal (age, diagnosis time, duration of the illness, BDI, BAI, HAM-D, HAM-A scores). Data were summarized in percentage, arithmetic mean, median and interquartile range (IRQ). BDI, BAI, HAM-D and HAM-A scores were compared using the Mann-Whitney U test and the Kruskal-Wallis analysis with regard to the severity of MG and treatment modality (prednisolone and drug combinations) (all tests were two-tailed). The relationship of anxiety/depression scale scores with the severity of MG and treatment modality was evaluated by Spearman's correlation analysis. Linear regression analysis (stepped) was performed to investigate the possible factors associated with mean HAM-D and HAM-A scores (as dependent variables). In single and double variable analysis, variables with a p value less than 0.05; gender (0=female, 1=male), severity of the illness (0=stage 1, 1=stage IIA, 2=stage IIB), treatment modality (0=only prednisolone, 1=prednisolone and azothioprine/pyridostigmine), and stressful life events were (0=yes, 1=no) recorded as independent variables.

Table 2. Comparison of mean anxiety and depression scale scores (standart deviations) with regard to myasthenia gravis severity

		MG severity			Kruskall-Wallis test
	Total	Stage I	Stage IIA	Stage IIB	p
BDI	15.0 (11.0)	11.5 (10.1)	14.9 (10.6)	18.5 (13.8)	0.41
BAI	8.2 (5.3)	4.0 (1.8)	7.8 (4.9)	13.1 (6.0)	0.01
HAM-D	14.9 (7.5)	10.6 (5.7)	14.2 (6.9)	21.4 (8.0)	0.02
HAM-A	18.2 (9.0)	12.5 (8.5)	17.4 (7.9)	26.3 (10.1)	0.03
psychic anxiety	6.2 (35)	4.6 (4.2)	6.3 (3.4)	7.4 (3.2)	0.46
somatic anxiety	11.9 (6.4)	7.8(5.5)	11.5 (5.2)	18.8 (7.4)	0.02

BDI: Beck Depresion Inventory, BAI: Beck Anxiety Inventory, HAM-D: Hamilton Depression Rating Scale, HAM-A: Hamilton Anxiety Rating Scale, MG: Myasthenia Gravis.

Table 3. Comparison of mean anxiety and depression scale scores (standart deviations) with regard to myasthenia gravis treatment modality

	Treatment		Mann-Whitney U test	
	Total	Prednisolone	Combination*	p
BDI	15.0 (11.0)	13.0 (10.1)	17.4 (11.8)	0.11
BAI	8.2 (5.3)	6.1 (4.0)	10.7 (5.7)	0.008
HAM-D	14.9 (7.5)	12.4 (6.5)	17.8 (7.7)	0.01
HAM-A	18.2 (9.0)	15.3 (7.8)	21.5 (9.4)	0.04
psychic anxiety	6.2 (35)	5.5 (3.7)	7.1 (3.2)	0.13
somatic anxiety	11.9 (6.4)	9.8 (4.9)	14.5 (7.2)	0.04

* prednisolone and azathioprine or pyridostigmine, BDI: Beck Depresion Inventory, BAI: Beck Anxiety Inventory, HAM-D: Hamilton Depression Rating Scale, HAM-A: Hamilton Anxiety Rating Scale.

Results

The age of the study population (n=42) ranged between 18 and 78 (mean: 42.6±17.6, median: 37, IQR: 28.7). Sociodemographic characteristics and illness-related data of the participants are summarized in Table 1. All participants were taking prednisolone at a mean dose of 33±26 mg/day, 17 participants were taking pyridostigmine at a mean dose of 220±110 mg/day and 8 participants were taking azathioprine at a mean dose of 166±40 mg/day. 19 participants were taking prednisolone plus azathioprine or pyridostigmine whereas 23 participants were receiving only prednisolone. 30 participants (71%) reported at least one stressful life event in the past six months. Mean BDI, BAI, HAM-D and HAM-A scores of the study population are shown in Table 2. The percentage of patients scoring above the cut-off point on BDI, BAI and HAM-D are 40.5%(n=17), 9.5%(n=4) and 52.4%(n=22), respectively. The Mann-Whitney U test was performed to investigate the presence of the difference between the scale scores with regard to gender. The results of the analysis indicated that female participants had significantly higher scores on BAI, HAM-A total, psychic and somatic than male participants (mean±SD: 9.6±5.4 vs 4.1±2, p=.001; 20.3±9 vs 12.2±6.1, p=.008; 7±3.5 vs 4.1±2.8, p=.03; 13.3±4.6 vs 8.1±3.9, p=.03, respectively). No significant difference was found between the mean BDI and HAM-D scores with regard to gender (p>.05). The Kruskal-Wallis test was performed to compare anxiety and depression scores with regard to marital status and educational status. No significant difference was found except for educational status and mean BDI scores. The mean BDI score of patients with less than 5-year education was 22±5, of patients with 6-to-8-year education was 15±12.5 and of patients with 9-to-11-year education was 10±5.1 (p=.02). Illness-related factors such as diagnosis time and duration of illness did not affect the mean anxiety and depression scores (p>0.05). Likewise, the Kruskal-Wallis test was performed to compare mean BDI, BAI, HAM-D and HAM-A scores with regard to disease severity (Table 2) and the Mann-Whitney U test was performed to compare the scores with regard to treatment modalities (Table 3). Participants with stage IIB MG had significantly higher scores on BAI, HAM-D, HAM-A total and somatic than those with stage I and II MG (p<0.05). Likewise, participants receiving prednisolone and pyridostigmine/azathioprine combination had significantly higher scores on BAI, HAM-D, HAM-A total and somatic than those receiving only prednisolone (p>0.05). Comparison of anxiety and depression scores between participants with or without stressful life events was performed by the Mann-Whitney U test. Participants with at least one stressful life event in the past six months had significantly higher scores on BDI and HAM-A psychic anxiety items than those without a stressful life event in the past six months (mean±SD: 17.1 vs 11.9, p=0.04; 7±3.6 vs 4.3±2.7, p=0.03, respectively). However, no difference was found with regard to mean BAI, HAM-D and HAM-A total and somatic scores (p>0.05). Two-variable analysis was performed to investigate the presence of correlation between age, severity of MG, treatment modality and anxiety/depression mean scores. Pearson analysis revealed no significant correlation between age and mean scores. Spearman analysis revealed a positive correlation between severity of MG and BAI, HAM-D and HAM-A total and somatic anxiety scores (Table 2). Spearman analysis also revealed a positive correlation between treatment modality and BAI, HAM-D and HAM-A total and somatic anxiety scores (Table 3). No correlation was found between severity of MG and BDI and HAM-A psychic anxiety scores (Table 2). No correlation was also found between treatment modality and BDI and HAM-A psychic anxiety scores (Table 3). Significant coefficients of two-variable analysis are shown in Table 4. Linear regression analysis of HAM-D revealed that severity of illness (B=5.36, p=0.006, Confidence Interval (CI) 95%[1.7-9.1]) and stressful life events (B=5.17, p=0.03, CI 95%[0.6-9.7]) were significantly associated variables (F=7.09, p=0.002). Severity of illness (B=6.17, p=0.005, CI 95%[2.0-10.3]), gender (B=-7.2, p=0.008, CI 95%[-12.5- -1.9]) and stressful life events (B=5.5, p=0.03, CI %95 [0.43-10.6]) were significantly associated factors when HAM-A total score was accepted as a dependent variable (F=8.07, p<0.001).

Discussion

In this cross-sectional study, the relationtionship of symptoms of anxiety and depression with severity of illness and treatment modalities was investigated among a cohort of patients with MG. Participants receiving medication combinations and those with more severe illness reported more symptoms of anxiety and depression.

Somatic complaints of MG patients may be misleading in terms of the accurate and correct diagnosis of psychopathology (21). Two previous studies (6,9) reported that patients should be carefully followed-up for psychiatric comorbidities following MG diagnosis. In a study by Magni et al. (6), point prevalences of affective disorder and anxiety disorder diagnosed by semi-structured interviews were found to be 32%and 5.5%, respectively. From this point of view, MG was considered a chronic and sometimes life-threatening disorder which causes significant emotional shift. However, coincidence of MG and psychiatric symptoms/disorders should not be ignored. In the present study, clinically significant depression was about 50%and anxiety was about 9%. The findings of the present study are in accordance with the previous reports using structured and semi-structured interviews. However, we did not use any structured interview in this study.

Findings on the relationship between severity of MG and psychiatric symptoms are conflicting. Paradis et al. (1993) (9) found

Table 4. The relation between MG severity, treatment modality and scale scores (Spearman analysis, rho)

	BAI	HAM-D	HAM-A	HAM-A somatic anxiety
MG severity	0.46*	0.42*	0.41*	0.42*
Treatment modality	0.42$	0.54$	0.4	0.38$

no relation between the severity of MG and psychiatric symptoms evaluated by the Symptom Check List-90 (SCL-90) and BDI. We also found no relationship between BDI scores and illness severity. On the other hand, participants with more severe MG reported more depressive symptoms on HAM-D and more anxiety symptoms on BAI and HAM-A than those with less severe MG. However, the most severely ill participants in the present study were at stage IIB according to the Osserman classification. Thus, no participant was admitted with the severe symptoms of respiratory crisis.

Another important point in a population with a medical diagnosis is the psychiatric adverse effects (AE) of medications used for treatment. In a previous study (7), higher depression scores were found to be associated with anticholinesterase medication doses. In the present study, participants receiving prednisolone and azathioprine/pyridostigmine combination were more depressive and anxious than those receiving only prednisolone (doses were not evaluated). This difference may be coincidental. Another explanation may be the drug-drug interactions or the AEs of pyridostigmine/azathioprine medications (22). Although anxiety, mania and psychosis are the well-known AEs of corticosteroid treatment (16), information about psychiatric AEs of medications used for the treatment of MG is limited. The cholinergic effects of anticholinesterase agents have been reported to play a role in the pathophysiology of depression in patients with or without MG (4). Third explanation is that patients with multi-drug treatments have more severe diseases and disability, and therefore, have more emotional disturbance. In the present study, female participants with MG were more anxious than their male counterparts. Participants with less than 5 years of education reported more depressive symptoms on BDI than those with more than 5 years of education. However, Magni et al. (1988) (6) failed to demonstrate an association between psychopathology and demographic features except gender. Magni et al. (6) also reported more severe psychopathology in females compared to males. Another finding of the present study is that participants who experienced a stressful life event in the past six months were more depressive and anxious (as assessed by BDI and HAM-A) than those who did not experience a stressful life event in the past six months. Regression analysis revealed that stressful life events were the factors associated with anxiety and depression in patients with MG. Despite methodological limitations, Magni et al. (1989) (23) reported that stressful life events had a negative effect on MG results. However, Magni et al. did not evaluate mood. Stressful life events may be extremely difficult to handle for patients with MG who are also struggling with the burden of the disease in terms of an unpredictable, chronic and life-threatening course.

Small sample size, lack of participants with advanced diseases, lack of evaluation with a structured interview based on DSM-IV-TR and the cross-sectional design of the study are the limitations of the present study. Furthermore, presence of a causal link between depression/anxiety symptoms, severity of illness and treatment modalities can not be established accurately based on the findings of this study. Are psychiatric symptoms reactive to severe MG and its treatment? Is this just a comorbidity case? Are these psychiatric symptoms the results of some neuroendocrine disturbances? To what extent individual emotional status or coping mechanisms, inadequate psychiatric evaluation or psychological support, social stressors, inadequate MG treatment or the direct effects on central nervous system beget psychiatric disturbances? More studies with more valid tools which evaluate more psychiatric symptoms/disorders focusing on medications (anticholinesterase and immunosuppressives), and on the results of psychopharmacological and/or psychotherapeutic interventions are needed. We think that clarifying the relationship between psychiatric symptoms and chronic/disabling autoimmune diseases such as MG is important. Unnecessary use of psychotropics following an inaccurate psychiatric diagnosis may worsen the course of MG. On the other hand, minor depression (depressive symptoms not meeting the DSM-IV-TR depression criteria) as well as major depressive disorders are associated with an increase in mortality and morbidity, as seen in multiple sclerosis, coronary heart disease and diabetes. There is limited evidence that these patients may benefit from psychotherapy techniques as well as psychotropic medications (10).

The findings of the present study suggest that patients with relatively more severe MG and patients receiving anticholinesterase-immunosuppressive combinations, some female patients and patients experiencing stressful life events may need careful psychiatric/psychological evaluation.

Acknowledgements

Authors would like to thank Prof Fazıl Guler for his advice on statistical analyses.

References

1. Craig TJ. An epidemiological study of a psychiatric liaison service. Gen Hosp Psychiatry 1982; 4:131-137.
2. Kulaksizoglu IB. Mood and anxiety disorders in patients with myasthenia gravis; aetiology, diagnosis and treatment. CNS Drugs 2007; 21:473-481.
3. McCabe MP, McKern S, McDonald E. Coping and psychological adjustment among people with multiple sclerosis. J Psychosom Res 2004; 56:355-361.
4. Keesey JC. Does myasthenia gravis affect brain? J Neuro Sci 1999; 170:77-89.
5. Hirschfeld RM, Keller MB, Panico S, Arons BS, Barlow D, Davidoff F, Endicott J, Froom J, Goldestein M, Gorman JM, Marek RG, Maurer TA, Meyer R, Philips K, Ross J, Schwenk TL, Sharfstein SS, Thase ME, Wyatt RJ. The National Depressive and Manic-Depressive Association consensus statement on the undertreatment of depression. JAMA 1997; 277:333-340.
6. Magni G, Micaglio GF, Lalli R, Belato L, Candeapo MR, Merskey H, Angelini C. Psychiatric disturbances associated with myasthenia gravis. Acta Psychiatr Scand 1988; 77:443-445.
7. Rohr W. Myasthenia gravis in the frontier of psychiatric diagnosis. Psyhiatr Praxis 1992; 19:157-163.
8. Perez-Nellar J, Rodriguez A. False negatives in the diagnosis of myasthenia gravis. Rev Nurol 2000; 30:712-715.
9. Paradis CM, Friedman S, Lazar RM, Kula RW. Anxiety disorders in a neuromuscular clinic. Am J Psychiatry 1993; 150:1102-1104.
10. Doering S, Henze T, Schussler G. Coping with myasthenia gravis and implications for psychotherapy. Arch Neurol 1993; 50:617-620.
11. Tucker DM, Roeltgen DP, Wann PD, Wertheimer RI. Memory dysfunction in myasthenia gravis: evidence for central cholinergic effects. Neurology 1988; 38:1173-1177.
12. Ossserman KE, Genkins G. Studies in myasthenia gravis: review of a twenty-year experience in over 1200 patients. Mt Sinai J Med 1971; 38:497-537.

13. BeckAT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4:561-571.
14. Hisli N. Beck Depresyon Envanteri'nin üniversite öğrencileri için geçerliliği güvenilirliği. Türk Psikoloji Dergisi 1989; 7:3-13
15. Beck AT, Epstein N, Brown G, Stear RA. An Inventory for measuring clinical anxiety: Psychometric properties. J Consulting and Clinical Psychology 1988; 56:893-897.
16. Ulusoy M, Şahin NH, Erkmen H. Turkish version of the Beck Anxiety Inventory: Psychometric properties. J Cogn Psychother 1998; 12:163-172.
17. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiat 1960; 23:56-62.
18. Akdemir A, Örsel S, Dağ İ. Hamilton depresyon derecelendirme ölçeğinin (HDDÖ) geçerliliği, güvenirliliği ve klinik kullanımı. Psikiyatri Psikoloji Psikofarmakoloji Dergisi 1996; 4:251-259.
19. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959; 32:50-55.
20. Yazıcı MK, Demir B, Tanrıverdi N, Karaağaoğlu E, Yolaç P. Hamilton Anksiyete Değerlendirme Ölçeği, değerlendiriciler arası güvenirlik ve geçerlik çalışması. Türk Psikiyatri Dergisi 1998; 9:114-117.
21. 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.
22. Ochs CW, Bradly RJ, Katholi CR, Byl NN, Brown VM, Jones LL, Shohet JS. Symptoms of patients with myasthenia gravis receiving treatment. J Med 1998; 29:1-12.
23. Magni G, Micaglio G, Ceccato MB, Lalli R, Bejato L, Angelini C. The role of life events in the myasthenia gravis outcome: a one-year longitudinal study. Acta Neurol Scand 1989; 79:288-291.