# Anxiety and depression symptoms in patients with generalized myasthenia gravis

## Jeneralize miyastenia gravis hastalarında anksiyete ve depresyon semptomları

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### ABSTRACT

**Objective:** Although there is an easily predictable relationship between psychiatric symptoms and myasthenia gravis, surprisingly few studies have evaluated this correlation. We aimed to screen the symptoms of anxiety and depression in generalized myasthenic patients using practical psychiatric scales and attract attention to the importance of these symptoms.

**Methods:** The correlations between the scores and age, gender, disease duration, intensive care unit experience, medications being used and the frequency of admission/hospitalization, Beck Anxiety , and Depression Scale (BAS, and BDS) scores of 30 patients (21 women), between 48-59 years of age were evaluated retrospectively.

**Results:** The BAS and BDS scores were found to be higher than the normal ranges in more than half of the whole patient group (56% and 60%, respectively). One third of all the patients required medical psychiatric treatment. The disease duration (RS: 0.68 and 0.56,p=0.016, for BAS and BDS,respectively), admission rate (RS: 0.66 and 0.46, p<0.001) and frequency of admission/hospitalization (RS: 0.64 and 0.48, p<0.001 for BAS and BDS,respectively) were statistically significantly related with the BAS and BDS scores.

**Conclusion:** The symptoms of anxiety and depression may easily mask the myasthenic symptoms, especially at the onset of the disease course leading to delayed diagnosis or misdiagnosis of myasthenia gravis. Furthermore, these symptoms may mimic the myasthenic symptoms in the disease course leading to over-treatments. Thus, inclusion of simple practical psychiatric scales in the evaluation of chronic autoimmune diseases as myasthenia in addition to neurologic evaluation would help in deciding the specific treatment strategies

**Keywords:** Myasthenia gravis, anxiety symptoms, depression symptoms

### ÖZ

**Amaç:** Anksiyete ve depresyon ile miyastenik semptomlar arasında kolayca tahmin edilebilecek bir ilişki olmasına karşın, literatürde konuyla ilgili şaşırtıcı şekilde az yayın bulunmaktadır. Bu araştırmada hastalarda anksiyete ve depresyon semptomlarının basit psikiyatrik ölçeklerle taranması ve bu semptomların önemine dikkat çekmek amaçlandı.

**Yöntem:** 48-59 yaş aralığındaki, 21'i kadın toplam 30 myastenik hastanın yaş, cinsiyet, hastalık süresi, yoğun bakım deneyimi, aldıkları tedavi ve tıbbi başvuru/hospitalizasyon sıklığı gibi parametreler ile Beck depresyon ve anksiyete skorları (BDS ve BAS) arasındaki ilişki retrospektif olarak değerlendirildi.

**Bulgular:** Olguların yarısından fazlası her iki ölçek için de normal kabul edilen sınırın üzerinde skorlar elde etti (BAS ve BDS için sırasıyla %56 ve %60) ve1/3'i yine her iki skor bakımından psikiyatrik tedavi gereksinimi kategorisinde yer aldı. Hastalık süresi (sırasıyla BAS ve BDS için r=0.68, 0,56 ve p=0,016) ve tıbbi başvuru/hospitalizasyon sıklığı anksiyete ve depresyon skorları ile anlamlı pozitif korelasyon (BAS ve BDS sırasıyla r=0,66, 0,46 p<0,001 ve r=0,64, 0,48 p<0,001) gösteriyordu.

**Sonuç:** Psikiyatrik semptomların hastalığın başlangıcında gerçek miyastenik bulguları maskeleyebileceği gibi tanı konduktan sonra ise onlara süperpoze olarak gereksiz hatta aşırı tıbbi uygulamalara yol açabileceği akılda tutulmalıdır. Bu nedenle myasteni gibi kronik otoimmun hastalıklar da hasta izleminin nörolojik değerlendirme yanında basit psikiyatrik ölçekleri de kapsaması doğru tedavi stratejilerin belirlemesine katkı sağlayabilir.

**Anahtar kelimeler:** Miyastenia gravis, anksiyetesemptomları, depresyon semptomları

## INTRODUCTION

Myastenia Gravis (MG) is a relatively rare antibody-mediated chronic autoimmune disease that occurs depending on the autoantibodies developed against the acetylcholine receptors on the neuromuscular junction and is characterized by weakness and quick exhaustion in bulbar and/or other voluntary muscles [1]. While, according to the Osserman classification, the disease is limited only to the ocular muscles in stage I patients and thus called as ocular MG (oMG), it is called generalized myasthenia gravis (jMG) if stiffness is experienced more or less in other voluntary muscles [1,2]. As is the case with many other chronic neurological diseases, it is known that the jMG has psychiatric symptoms, but there are a limited number of studies in the literature in which the frequency of such symptoms and their effect on disease progression are examined. However, the relationship between the psychiatric symptoms and myasthenia is particularly important in some cases and thus it should be borne in mind. First of all, complaints such as quick exhaustion, lack of energy, weakness and air hunger are the symptoms that can easily be associated with psychiatric reasons. The fact that such complaints fluctuate within the day and sometimes they go away on their own or heal completely makes it easier to make psychiatric diagnoses [4,5]. The other side of the coin suggests, however, that the same complaints may have the potential to get confused with the real myasthenia symptoms once a jMG diagnosis has been made and thus require unnecessary or even extreme medical interventions as a result [5,6]. Under the light of these facts, therefore, it is clear that the psychiatric symptoms in the jMG patients should be paid a special attention.

In this study, the frequency of the anxiety-depression symptoms in the jMG diagnosed cases, the reasons with which they may be associated, and the relationship between seeking medical help and hospitalization frequency have been examined.

## MATERIAL and METHOD

This study has been conducted with a total of thirty patients, 21 women and 9 men, with jMG diagnosis and average age group of 53±14.6 (aged between 48 and 59) based on medical history, neurological treatment, electrophysiological tests (repetitive EMG, single fiber EMG) and the presence of acetylcholine receptor antibodies. The patients in stage II, making up 53% of the group (16 cases), and in stage IIb, making up 47% of the group (14 cases), -as per Osserman [7] classification- have been informed as to the nature of the study and submitted their informed consent forms. Beck depression [8] and anxiety [9] scales were applied to all of the cases. Those with coexisting diseases such as cerebrovascular diseases, epilepsy, Parkinson disease and dementia were excluded from the study. All the systemic diseases and mood disorders save for controlled hypertension, antidiabetic and regulated diabetic and such psychiatric disorders as chronic psychotic disorder were considered as exclusion criteria. The cases with stage I pure ocular stiffness as per Osserman classification were excluded from the scope of this study. Patients in stage III and above conditions, as per Osserman classification, with increased physical immobility were not included in this study. As a result of the implementation of the aforementioned parameters the cases included in this study were limited to thirty. Therefore, a relatively homogenous group was created, consisting of Osserman Stage IIa and IIb jMG patients. According to the Beck anxiety scores (BAS), the scores between 0 and 7 were considered as normal, 8 and 15 as mild, 16 and 25 as medium, and 26 and 63 as severe anxiety symptoms. According to Beck depression scores (BDS), the scores between 0 and 9 were considered as normal, 10 and 16 as mild, 17 and 20 medium and 30 and 63 as severe depression symptoms.

The patients with medium and severe symptoms in both groups were taken into a psychiatric treatment requirement (PTR) category. In addition to the duration of disease, disease stage, medication being taken,

intensive care history, thymectomy and antibody presence, the breakdown of the patients included the frequency of seeking medical help and hospitalization for the last one year.

The relationship between the identified parameters, demographic characteristics and the BAS and BDS were evaluated by using the SPSS 19.0 software. Chi square test was conducted to evaluate the categorical data. The compatibility of variables to the normal distribution was reviewed through Shapiro Wilk test. Student's t test and Mann-Whitney U test were used to evaluate the parametric and non parametric data. A one way variance analysis was used to compare more than two groups. The relationship between the variables was evaluated by conducting Spearman and Pearson correlation tests. The significance limit was considered to be $p < 0.05$.

### RESULTS

The average duration of disease of the cases included in the study was found to be 8.5±6.8 (2-26) years. While 27 of them (90%) were acetylcholine receptor (Ach) antibody positive, 16 of them (53%) were in Osserman stage IIa, and 14 of them (47%) were in stage IIb. While 18 cases (60%) said they had intensive care experience due to myasthenic deterio-

ration/myasthenic crisis; while 16 cases (53%) were found to have undergone a thymectomy operation, 14 of them (47%) had no thymectomy operation previously. The descriptive features of the cases are summarized in Table 1. Treatment groups were formed based on the consideration that the treatments being used might have an impact on the BAS and BDS. All of the patients participating in the study were taking oral pridostigmine. While 2 patients (6.7%) were taking only pridostigmine, 9 of them (30%) were additionally taking lower doses of oral corticosteroid, 11 of them (36.6%) were taking intravenous immunoglobulin (IVIG) on an additional and intermittent basis, 6 of them (20%) were taking azatiopurine in addition to pridostigmine, and 2 of them (6.7%) were taking IVIG on intermittent basis in addition to the said medication (Figure 1). No statistically significant relationship was established between the said treatment protocols and the anxiety and depression scores ($p > 0.05$). When all the groups were considered the average BAS score was found to be 13.1±10.4 (3-39), whereas the average BDS score was found as 13.4±8.8 (2-32). In terms of anxiety, 13 of the cases (44%) were found to be in normal, 7 (23%) in mild, 6 (20%) in medium and 4 (13%) in severe category; In terms of depression, however, 12 of the cases (40%) were found to be in normal, 8 (26.6%) in mild, 7 (23.3%) in medium and 3 (10.1%) in severe category. Based on the aforementioned scores, one third of the study population was found to have advanced levels of anxiety and depression symptoms that required treatment (Table 2).

**Table 1. Descriptive characteristics of the cases.**

| | |
|---|---|
| Age (avg±SD) year | 53±14.9 (48-59) |
| Duration of disease (avg ± SD) year | 8.5±6.7 (2-26) |
| Gender F/M | 70/30 |
| Osserman classification | |
| Stage IIa | 16    53 |
| Stage IIb | 14    47 |
| Ach Receptor antibody +/- | 27/3   90/10 |
| Presence of thymectomy Yes/No | 16/14   53/47 |
| Intensive care history Yes/No | 18/12   60/40 |
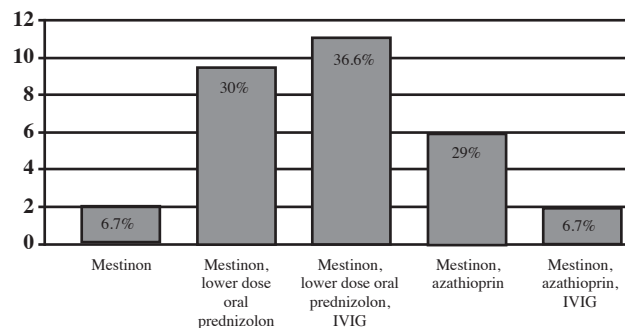


**Figure 1.** Distribution of the cases in accordance with the applied medical treatment.

**Table 2. Distribution of BAS and BDS values of the cases.**

| | Beck Anxiety Score (BAS) (average 13±10.4) | | | Beck Depression Score (average 13.4±8.8) | | |
|---|---|---|---|---|---|---|
| | Cases | | | Cases | | |
| | Score Scale | Number | % | Score Scale | Number | % |
| | Normal (0-7) | 13 | 43.4 | Normal (0-9) | 12 | 40.0 |
| | Mild (8-15) | 7 | 23.3 | Mild (10-16) | 8 | 26.6 |
| Psychiatric treatment requirement | Medium (16-25) | 6 | 20.0 | Medium (17-29) | 7 | 23.3 |
| | Severe (26-63) | 4 | 13.4 | Severe (30-63) | 3 | 10.1 |

The aforementioned data was also evaluated in terms of the relationship between the treatment applications and depression-anxiety symptoms as well as the frequency of seeking medical help and hospitalization in the last one year. While no significant relationship was established between the BDS and gender, the relationship between females and BAS was statistically significant (p=0.013). Moreover, according to BAS 42.8% of the female patients and 11.1% of the male patients were found to be in the PTR (psychiatric treatment requirement) category; according to BDS scores, however, 47.6% of the female patients were in the said category, while no male patient was found to be in the PTR category as per BDS. A positive correlation was identified between the duration of disease and BAS and BDS (respectively rs 0.68, 0.56, p<0.001). The relationship between age, antibody presence, thymectomy, applied treatment protocol and anxiety and depression symptoms was not statistically significant. But the intensive care unit history was found to be associated with high BAS and BDS scores (respectively p=0.018, p=0.021). A statistically significant positive correlation was identified between BAS and BDS as well (respectively rs 0.95, 0.84, p<0.001). When the patients were evaluated in terms of their frequency of seeking medical help and hospitalization in the last one year, it was observed that the annual frequency of seeking medical help was 4.3±3.1, while the annual frequency of hospitalization was 1.5±2.1. Such parameters were found to have a significant relation-

ship with BAS (respectively 0.66, 0.46, p<0.001) and the same relationship was also the case for BDS (respectively 0.64, 0.48, p<0.001). Those with high BAS and BDS scores had higher frequency of seeking medical help and hospitalization. The relationship between other parameters –including age, gender, duration of disease, thymectomy and antibody presence, intensive care history and applied medication- and the frequency of seeking medical help and hospitalization was not statistically significant.

## DISCUSSION

Myasthenia gravis is an antibody mediated prototypical autoimmune disease developed against the post synaptic acetylcholine receptors on the neuromuscular junction [1, 2]. The effects of the disease on the areas associated with central cholinergic system such as human behavior, sleep patterns and memory as well as its relationship with the immunological mechanisms resulting from behavioral changes as in the case of other autoimmune diseases have been areas of interest for a number of research studies [10-13]. However, the chronic, destabilizing, life threatening and unpredictable progression of the generalized form of the disease in particular overshadows the psychiatric symptoms, and thus it is difficult to suggest that the said symptoms are sufficiently taken into consideration in the daily medical practice [5,14]. The fact that some medicines are known to have potential to cause myasthenic deterioration is yet another factor that

serves to make the issue a taboo [3,5].

The asymmetrical, daily fluctuating and, in some cases, self-healing muscle weakness observed in the myasthenia cases may at least result in a psychiatric diagnosis at the outset [4,13-15]. While Rohr et al. reported that one fifth of the myasthenic patients were diagnosed with a psychiatric disorder at the beginning, Perez-Nellar et al. suggested that only 9% of the cases were correctly diagnosed with the disease in the initial medical consultation [15,16]. There are publications in the literature that suggest that the myasthenic patients may, albeit rarely, be observed with a psychiatric disorder until it is necessary to introduce intubation [4]. As a matter of fact, stressful life events can be included in the patient's medical history in the case of autoimmune diseases, and they are explained through their role in the development of immune dysregulation and autoimmunity via hypothalamo-hypophysio-adrenal axis glucocorticoid and catecholamines [4,13,17].

Despite the studies reporting that the MG patients show various psychiatric symptoms, particularly depression and anxiety symptoms, more than other patients [3,17], there are nevertheless studies that conflict with this view [18]. Moreover, while some of the studies give prominence to the symptoms of anxiety [6,19], some other studies give prominence to the symptoms of depression [17,20]. The present study has been conducted on a relatively homogenous group of patients, consisting of Osserman classification stage IIa and stage IIb patients, which group has been further diminished with the exclusion of patients with rare and coexisting systemic, neurological and psychiatric disorders. There are studies in the literature with much bigger sample sizes than this study [17-19]. We believe that the fact that such studies put the cases with periocular stiffness in the same category as stage III and above patient groups presents an equally great disadvantage as having a small sample size. In this study, having a small sample size is a non negligible limitation that serves to increase the type II error possibility especially with respect to sub groups. However, the fact that both scores were found to be

higher than normal values in more than half of the cases (BAS and BDS respectively 56% and 60%) and that more than half of such cases were included in the psychiatric treatment requirement (PTR) category is considered to be significant.

Our findings are also consistent with those included in the literature, in that the BAS value that was found to be higher than normal values in 55% of the cases by Lundeen et al. was determined as 56.7% in this study. This can be taken as a proof that the methodology employed in this study was reliable. While the difference between the incidents of the symptoms of anxiety and depression was not found to be statistically significant, a statistically significant, strong and positive correlation was nevertheless established between the BAS and BDS values (respectively rs 0.95, 0.84, p<0.001). This particular finding can be interpreted as the symptoms of anxiety and depression triggering each other for the patient groups participating in the study. There are also studies in the literature that suggest the existence of a significant relationship between the presence of psychiatric symptoms in myasthenic patients and female gender [17,21]. While we have failed to establish a significant difference between the genders in terms of BDS values, BAS values were found to be highly and statistically significant in the female patients (p=0.013). While the present study has established a statistically significant relationship between the duration of disease and the symptoms of anxiety and depression (respectively rs 0.68, 0.56 and p=0.016 for BAS and BDS values) in line with the finding of the literature [3,6,20], no statistical significance was established between the relationship with said findings and the severity of the disease since only the Osserman stage II cases were included in the study. As a result of the assessment of the study results, the scores of the cases that had been previously observed in the intensive care unit due to myasthenic crisis, deterioration or the possibility thereof, without necessarily having a tracheal intubation-ventilation experience, were found to be higher than others, which was determined as statistically significant for bother scores (value for

BAS and BDS respectively p=0.018, p=0.021).

In MG, the applied treatment is another issue that needs to be assessed in terms of its relationship with the psychiatric symptoms. For instance, the use of corticosteroids (CS) is known to cause a number of disorders, including delirium and psychosis [22,23]. Chronic use of lower doses as in the case of myasthenia is known to be associated with depression, while short term use of higher doses is known to be associated with euphoria-hypomania [5,22,23]. Some studies suggest that the use of steroids in myasthenics did not change the frequency of psychiatric findings [3,5,17]. In our study, however, the variance in treatment protocols serves to increase the type II error possibility. For this reason, evaluating the scores in accordance with the treatment groups will not significant in statistical terms. The relationship between the BAS and BDS values and the frequency of seeking medical help and hospitalization, which constitutes the peculiar part of our study, reveals interesting results. While the frequency of seeking medical help and hospitalization had no statistically significant relationship with such parameters as age, gender, duration of disease, thymectomy and presence of Ach antibody, YBD and applied treatment, it nevertheless showed a statistically significant positive correlation with the BAS and BDS values (BAS and BDS values respectively rs 0.66, 0.46 p<0.001 and 0.64, 0.48 p<0.001). Such a result points out to the importance of correctly recognizing the symptoms of anxiety and depression in a disease like myasthenia which is fraught with high treatment costs and risky treatment option [24].

In summary, the often neglected symptoms of anxiety and depression are observed abundantly in the patients of jMG and they require psychiatric treatment in a significant number of cases. Such findings may imitate the real myasthenic symptoms and show a statistically significant relationship with the frequency of seeking help and hospitalization. Periodic use of simple, reliable and valid psychiatric scales in the medical centers where the jMG cases are observed will be beneficial in terms of recognizing such symptoms. Recognizing treatable psychiatric symptoms is particularly important both in terms of identifying the real indications of the risky and costly treatment protocols peculiar to the disease and improving the life quality of the patients.

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