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Original Article / Özgün Araştırma

Presence of Concomitant Depression and its Effect on Clinical Course in Patients Diagnosed with Myasthenia Gravis

Myastenia Gravis Tanılı Hastalarda Hastalığa Eşlik Eden Depresyonun Varlığı ve Klinik Seyre Etkisi

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Abstract

Objective: Myasthenia gravis (MG) is a chronic autoimmune disease with fluctuating non-specific symptoms, and symptoms are exacerbated by stress. Many psychiatric disorders, especially depression, may accompany MG. This study aimed to determine the presence of depression accompanying MG and the effect of depression on the clinical course.

Materials and Methods: Ninety-eight patients were diagnosed with MG between the ages of 18 and 65 who had a follow-up of at least 1 year at Ege University Faculty of Medicine, Department of Neurology, Muscular Diseases Outpatient Clinic and who did not have any medical or psychiatric illness that prevented communication were included in our study. Instead, of using questionnaire forms to diagnose depression, a one-to-one interview method following Structured Clinical Interview for DSM-IV Criteria (SCID-1) was preferred. The clinical course of patients with and without depression and their responses to standard symptomatic or immunosuppressive therapy was evaluated using the MG treatment response rating scale by the lead investigator, who was blind to the presence of depression in patients.

Results: In the SCID-1 evaluation of our patients, depression was detected in 40.8% of the patients. Of our patients, 64.9% identified a stressor factor before the onset of disease symptoms. In the evaluation of treatment response, 19.4% of our patients had remission, and 80.6% had minimal symptoms. In evaluating the change in the clinical situation, improvement was detected in 88.8% of the patients. A statistically significant relationship was found between worse treatment response and depression (p=0.018).

Conclusion: It was determined that depression was frequently present in patients with MG and the clinical course was worse in patients with depression. Therefore, it was aimed to draw attention to the importance of detecting depression in patients with MG and that treatment regulation in this direction might positively affect the course of the disease.

Keywords: Myasthenia gravis, depression, clinical course

Öz

Amaç: Myastenia gravis (MG) dalgalı seyreden non-spesifik semptomları olan, semptomları stres ile alevlenen, kronik otoimmün bir hastalıktır. MG'ye depresyon başta olmak üzere birçok psikiyatrik hastalık eşlik edebilir. Bu çalışmada, MG'ye eşlik eden depresyon varlığının ve depresyonun klinik gidişe olan etkisinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Ege Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı Kas Hastalıkları Polikliniği'nde en az 1 yıllık takipleri olan, 18-65 yaş aralığında olan, iletişim kurmaya engel herhangi bir tıbbi ya da psikiyatrik hastalık durumu olmayan 98 MG tanılı hasta çalışmamıza dahil edilmiştir. Depresyon tanısı konulması için anket formlarının uygulanması yerine, birebir görüşme yöntemi olan DSM-IV ölçütlerine yönelik yapılandırılmış klinik görüşme (SCID-1) tercih edilmiştir. Depresyonu olan ve olmayan hastaların klinik gidişleri, standart semptomatik veya immünosüpresif tedaviye yanıtları MG tedavi yanıtı değerlendirme skalası kullanılarak, hastalarda depresyon varlığı konusuna kör olan baş araştırmacı tarafından değerlendirilmiştir.

Bulgular: Hastalarımızın SCID-1 değerlendirmesinde %40,8 oranında depresyon tespit edilmiştir. Hastalarımızın %64,9'u hastalık bulgularının başlangıcından önce stresör bir faktör tanımlamışlardır. Tedavi yanıtı değerlendirilmesinde hastalarımızın %19,4'ünde remisyon, %80,6'sında minimal belirtiler saptanmıştır. Klinik durumda değişimin değerlendirilmesinde %88,8 oranında iyileşme tespit edilmiştir. Depresyonu olan hastalarda tedavi yanıtının daha kötü olduğu yönünde istatistiksel anlamlı ilişki saptanmıştır (p=0,018).

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Sonuç: MG tanılı hastalarda depresyonun sıklıkla birlikte bulunduğu ve depresyonu olan hastalarda klinik seyrin daha olumsuz olduğu tespit edilmiştir. Bu nedenle MG'li hastalarda depresyonun tespitinin önemine ve bu yönde tedavi düzenlenmesinin hastalık seyrine olumlu etkisinin olabileceğine dikkat çekmek amaçlanmıştır.

Anahtar Kelimeler: Myastenia gravis, depresyon, klinik gidiş

Introduction

Myasthenia gravis (MG) is a chronic disease caused by autoimmune impairment of the postsynaptic acetylcholine receptors (AChR) of the neuromuscular junction. It is characterized by muscular weakness in striated muscles and abnormal fatigue showing a wavy course, increasing with movement and decreasing with rest. MG is a disease that can be seen in all ages and genders, and it is more common in women at younger ages. It is the most common neuromuscular junction disease (1,2). The clinical symptoms of MG are non-specific and fluctuate, and symptoms such as speech impairment, isolated or generalized muscle weakness, and chronic fatigue can be exacerbated by stress. These variable features of symptoms and their aspects, such as causing increased social isolation, attract attention as common features with psychopathological diseases. These features may cause patients to be initially misdiagnosed with a psychiatric disease such as conversion disorder or depression (3,4). In addition, psychiatric disorders can be seen as the first symptom of MG (5). It is stated that psychiatric symptoms are expected in patients during the disease due to the chronic and life-limiting course of MG at an unpredictable rate (6,7,8).

For this reason, it is essential to make a correct diagnosis of psychiatric disease accompanying MG and to treat and follow-up patients in this respect. Emotional stressor factors are important factors that worsen myasthenic symptoms (6,7,8,9). The necessity of long-term use of corticosteroids and immunosuppressant agents with known psychopathological side effects in MG treatment and the adjustment of drug doses according to the clinical condition of patients increases the importance of detecting the presence of psychopathology accompanying the disease and considering this factor in the treatment plan.

Symptoms seen in depression occurring secondary to any primary disease cannot be distinguished from primary depression. In cases of secondary depression; depression is not the primary disease that directly affects the brain, but depression is due to the adding of comorbid causes, which are the results of the effects of psychosocial stress, fears, anxieties, and feelings of helplessness caused by the disease, to the actual disease (10). Conditions that occur with diseases directly affecting the brain and improve when the disease is eliminated are called organic depression in International Classification of Diseases-10 (ICD-10), as depression due to general medical condition or as depression due to substance abuse or physiological condition in Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) (11,12). It has also been suggested that there is no one-to-one causal relationship between many diseases, pharmacological agents, and major depression that are thought to cause depression and that a physical disease or drug is a trigger in predisposed individuals (5,13). Some studies show that besides MG's nature, corticosteroids and immunosuppressive drugs used in the treatment of MG for a long time can also cause depression. The frequency of depression is associated with the dose of medication (5,13,14,15).

The etiology of psychiatric symptoms seen in MG is not known. The possibility of central nervous system (CNS) involvement in MG has not been examined in detail. The data on the CNS effect in MG obtained in the few studies conducted have not been convincing. It has been concluded that psychiatric disorders may occur in patients as an expected result of the chronic disease process due to MG's chronic and unforeseen life-limiting clinical course (13,14,16).

There are few studies conducted in recent years on psychiatric symptoms or disorders seen in patients with MG. Therefore, in this study, it was aimed to determine the presence of depression accompanying MG in patients with MG, to determine the clinical and sociodemographic characteristics of patients with and without depression, to examine the clinical response to the standard treatments used, and to investigate the effect of the presence of depression on the clinical course. In addition, it was aimed to draw attention to the fact that treatable psychiatric symptoms or disorders that might accompany MG could often coexist with the disease, and to ensure that this factor, which might have an impact on the clinical course, was also taken into account during the treatment of patients.

This study hypothesizes that depression is often seen together with MG in patients. The clinical course of patients without depression is better than that of patients with depression.

Materials and Methods

Our study was carried out as a prospective clinical study between 2010 and 2011. Our study was conducted with patients between the ages of 18 and 65 who had at least 1-year follow-up in the Muscular Diseases Outpatient Clinic of the Department of Neurology of the Ege University Faculty of Medicine, and who did not have any medical or psychiatric diseases that prevented healthy communication during the mutual interview. Patients who received psychiatric treatment for the last 1 year were excluded from the study to eliminate the false negative effect of the depression treatment in determining the depression accompanying MG and its possible misleading impact on the clinical course. Ninety-eight patients who met the study criteria among 335 MG patients enrolled in our muscular diseases outpatient clinic were included in our study. Informed consent was obtained from all patients, and study approval was obtained from Ege University Ethics Committee (decision no: 10-5/10, date: 27.05.2010). The patients were recorded with their sociodemographic characteristics, clinical conditions, and treatments they were receiving.

Study Scales

All patients included in our study were classified using MG classification according to their examination findings. The patients were diagnosed with depression or other psychiatric

diseases with a psychiatric diagnostic module, Structured Clinical Interview for DSM-IV Criteria (SCID-1), of which validity and safety in Turkish were studied. The assessment was made using the one-to-one interview method. Patients with psychiatric disorders were directed to Ege University Psychiatry Department Consultation-Liaison Unit to complete their treatment and follow-up. The clinical courses of the patients, which were determined by evaluating the current clinical conditions of the patients with and without depression and comparing them with their previous clinical conditions, and responses to standard symptomatic or immunosuppressive therapy were evaluated by the lead investigator who was blinded for the presence of depression in the patients using the MGFA post-intervention status. According to this scale, it is accepted that patients with remission have a positive treatment response.

Statistical Analysis

The obtained data were analyzed using Statistical Program for Social Sciences-SPSS-15.0 in the Department of Biostatistics and Medical Informatics at Ege University Faculty of Medicine. The significance level was accepted as $p<0.05$ in statistical evaluations. Crosstables were created for categorical data, and χ^2 analysis was made. Student's t-test and Mann-Whitney U test were used for comparison of groups with continuous variables. Kruskal-Wallis analysis was used for multigroup comparison.

Results

In Table 1, besides the sociodemographic characteristics of the patients included in the study, the clinical features and course of MG and the parameters associated with the development of depression are presented. The ages of the patients included in the study were between 20 and 65, and the average age was 43.97±12.5 years. Of the patients, 67.3% were female, and 32.7% were male. Of our patients, 34.7% completed primary school, 32.7% college or university, and 31.6% secondary school. Although it was observed that our patients belonged to entirely different occupational groups, it was found that 42.9% were housewives. Our patients stated their socioeconomic status as 74.2% medium, 20.4% good, and 5.1% bad. In our study, the first complaint was ptosis with a rate of 70.4%, followed by fatigue with a rate of 53.1%. Diplopia was found in 33.7%, dysphagia in 27.6%, limb weakness in

Table 1. Demographic and clinical characteristics of patients with myasthenia gravis

		N	%
Gender	Female	66	63.7
	Male	32	32.7
Education status	Primary school	34	34.7
	Secondary school	31	31.6
	Higher education	32	32.7
Socioeconomic status	Very good	0	0
	Good	20	20.4
	Moderate	73	74.5
	Bad	5	5.1
Concomitant autoimmune disease		11	11.2
Thyroid pathology	No	67	68.4
	Hypothyroidism	11	11.2
	Nodule	14	14.3
	Hashimoto Thyroiditis	6	6.1
Thymus pathology and thymectomy status	Thymus normal Thymectomy +/-	17/56	17.3/57.2
	Thymic hyperplasia Thymectomy +/-	7/5	7.1/5.1
	Thymoma Thymectomy +	13	13.3
Antibody status	Anti ACH R +	42	42.9
	Anti MuSK +	2	2
	Antibody -	26	26.5
	Unknown	28	28.6
Complaint at first admission	Ptosis	69	70.4
	Tiredness	52	53.1
	Diplopia	33	33.7
	Difficulty swallowing	27	27.6
	Limb weakness	25	25.5
	Difficulty speaking	19	19.4
	Difficulty in chewing	16	16.3

AChR: Acetylcholine receptors, MuSK: Muscle-specific kinase

25.5%, difficulty speaking in 19.4%, and chewing difficulty in 16.3% as the first complaint. Of the patients, 69.4% identified a stressor factor in the period just before the onset of the disease symptoms. When the thymus pathologies associated with MG were examined, the thymus was evaluated as normal in 74.4% and pathological in 25.6%. Thymic hyperplasia was detected in 12.2% of the pathological group, and it was found that thymectomy was applied in 24.4% of these patients and 13.3% of the patients with thymoma. The rate of autoimmune disease accompanying MG was 11.2%, and thyroid pathology was detected at a rate of 31.6%. Antibody measurements were made in 71.4% of our patients and 60% of these patients were positive for AChR antibody, 37.1% were negative for AChR antibody, and 2.9% were positive for muscle specific kinase antibody. The presence of antibodies was unknown in 28.6% of the patients.

Chart 1 shows the distribution of the clinical conditions of the patients included in our study according to the MG classification and whether the disease is accompanied by depression or not. According to the MG classification, 32.7% of our patients had class I, 20.4% class IIa, 29.6% class IIb, 11.2% class IIIb, 4.1% class IVb, 1% class IIIa and IVa MG, and there were no patients with class V MG. While the rates of patients with and without depression were close to each other and high in class I, IIa, and IIb patients (22.5%, 17.5%, and 27.5%, respectively), depression was found in lower rates in class IIIb, IVa, and IVb patients (20%, 2.5%, and 7.5%, respectively).

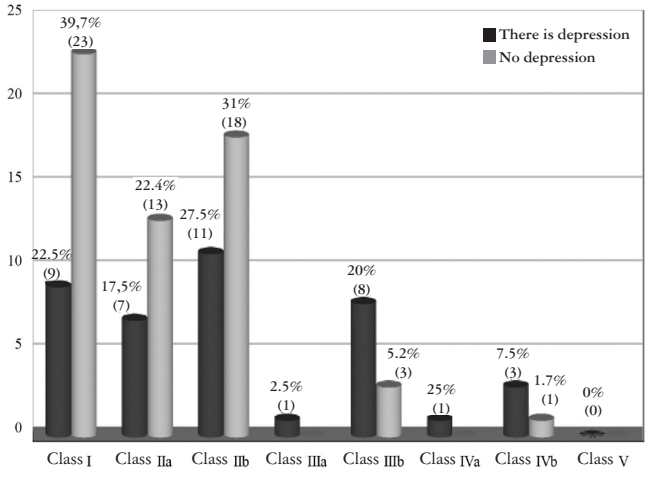

Chart 1. Classification of patients with myasthenia gravis according to presence of depression
Class I: *Eye muscle weakness*
Class II: *Mild weakness in extraocular muscles*
IIa: Dominant weakness of the limbs, trunk muscles, or both
IIb: Weakness in the oropharyngeal, respiratory muscles, or both
Class III: *Moderate weakness in the extraocular muscles*
IIIa: Dominant weakness of the limbs, trunk muscles, or both
IIIb: Weakness in the oropharyngeal, respiratory muscles, or both
Class IV: *Severe weakness in extraocular muscles*
IVa: Dominant weakness of the limbs, trunk muscles, or both
IVb: Weakness in the oropharyngeal, respiratory muscles, or both
Class V: *Intubation status with or without mechanical ventilation need*

Chart 2 shows the depression rates determined as a result of the evaluation of our patients with SCID-1. While no psychopathology was detected in 44.9% of our patients, depression was detected in 40.8%.

Of our patients, 99% used cholinesterase inhibitor, 91.8% oral corticosteroid, 25.5% azathioprine, 2% cyclophosphamide, 1% mycophenathyl mofetil for the treatment of MG, and 2% of them received plasma exchange therapy. When the lifelong use of antidepressant medication was questioned, 26.7% of the patients stated that they used antidepressant treatment in any period except the last one year. In the evaluation of treatment response, it was observed that remission was achieved in a total of 19.4% of our patients, including 4.1% with complete remission without medication. Their last clinical evaluations determined that 80.6% of the patients had minimal symptoms, and 42.5% received symptomatic and immunosuppressive treatment. Table 2 shows the assessment of treatment response and change in clinical status in patients with and without depression. It was found statistically significant that treatment response was worse in patients with depression (p=0.018). In addition, a statistically significant correlation was found between worse treatment response and fatigue at presentation (p=0.044). There was no relationship between treatment response and patients' age, gender, educational status, professions, socioeconomic levels, ages of symptom onset, presence of thyroid disease and other autoimmune diseases, thymus pathologies, thymectomy status, antibody status, MG class, agents used in treatment, presence of stressor factors before the onset of symptoms, and antidepressant use in the past (p<0.05). In evaluating the change in the clinical situation, 88.8% of our patients recovered, 5.1% exacerbated, while 6.1% did not have a significant difference in clinical findings compared to the baseline.

Discussion

For a long time, it has been known that depression or other psychopathologies are common in patients with MG, and this association has been expressed in many studies. In particular, the preventive clinical features and chronic course of MG have been shown as the cause. However, it is noteworthy that in these studies, self-reporting questionnaires have been used as a screening

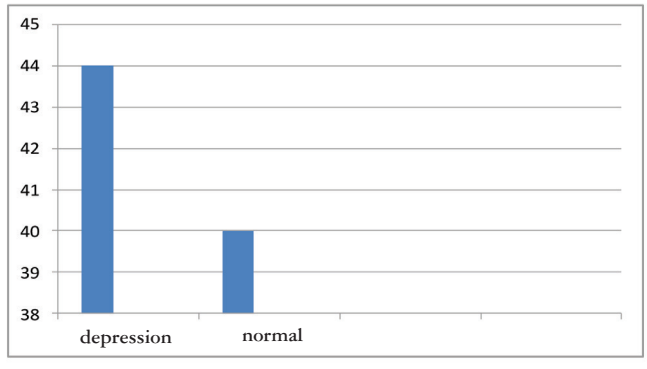

Chart 2. Depression rate in patients with myasthenia gravis*
**Depression was found in 44.9% patients (n=44) included in the study, and no depression was found in 40.8% patients (n=40)*

Table 2. MGFA* change in treatment response and clinical status						
	Depression (+)		Depression (-)		Total	
	N	%	N	%	N	%
Treatment response status						
Complete stable remission	0	0	4	6.9	4	4.1
Pharmacological remission	3	7.5	12	20.7	15	15.3
Minimal symptom 0	2	5.0	0	0	2	2
Minimal symptom 1	12	30.0	19	32.8	31	31.6
Minimal symptom 2	2	5.0	2	3.4	4	4.1
Minimal symptom 3	21	52.5	21	36.2	42	42.9
Change in clinical situation						
Improvement	34	85	53	91.4	87	88.8
No change	3	7.5	3	5.2	6	6.1
Worsening	0	0	0	0	0	0
Exacerbation	3	7.5	2	3.4	5	5.1
Death due to MG	0	0	0	0	0	0

*MGFA: Myasthenia Gravis Foundation of America, MG: Myasthenia gravis

method, and the effect of the detected psychopathology on the clinical course has not been examined. In this study, the presence of depression accompanying MG was determined by the clinical interview method. In addition, the effect of the existence of depression on the clinical course was tried to be determined. In our study, the coexistence of MG and depression was detected at a rate of 40.8%. It was found that the presence of depression had a statistically significant adverse effect on the clinical course.

In previous studies, Magni et al. (3) evaluated 74 patients with MG using DSM-III diagnostic criteria. They stated that among the psychopathologies they detected at 51%, the affective disorder was the most common with a rate of 32%. Fisher et al. (17) detected various typical somatic and psychological depression symptoms in 33% of 45 patients with MG by evaluating them with the Beck depression inventory (BDI), a self-administered questionnaire method. In one of their studies, Doering et al. (18) evaluated 44 patients with MG according to ICD-10. They reported that 41% had at least one psychiatric diagnosis, and the most common diagnosis was long-term reactive depression, with a rate of 15.9%. Another study found that 50% of patients with MG had depression by using the BDI and the Hamilton depression scale (16). Unlike other studies in which self-answered inventories were used, In the study by Ybarra et al. (14), in which clinical interview method was used similar to our study and 41 MG patients were examined in terms of psychopathology, depression was found with a rate of 40.2%, 17.1% of which was major depression. The questionnaire method, which is used in many studies to determine the presence of depression, such as the BDI, was not preferred by us because it was structured to screen depression, the patients answered questions on their own, and the patients could not understand or misunderstand the questions which would negatively affect the clinical interpretation. In many studies, researchers stated that using a self-answered inventory to detect psychopathology was a limitation of their studies (15,16). In our study, in order to detect depression, SCID-1 was administered by the investigator through one-to-one interviews with patients. To eliminate the association of depression with MG and the potentially misleading effect of depression treatment on the clinical course of MG, patients who received or were receiving antidepressant or supportive psychiatric treatment for 1 year before the evaluation were excluded from the study, and the depression rate accompanying MG was tried to be determined. In our study, the depression rate accompanying MG was found to be 40.8%.

In our study, when examined according to clinical findings, the milder groups (class I, IIa, and IIb) had a higher rate of depression (22.5%, 17.5%, and 27.5%, respectively) than the clinically more severe groups (class IIIb, IVa, and IVb) (20%, 2.5%, and 7.5%, respectively). Our patient numbers in group IVa and IVb were 1 and 4, respectively. Depression was present in 1 patient in group IV (100%), and depression was detected in 3 (75%) of 4 patients classified as group IVb. Thus, in terms of the total number of patients, the number of patients with more severe diseases in our study was lower than those with milder diseases. Still, comorbidity of depression was more pronounced in severe patients.

The aggravating effect of stressor factors on MG symptoms and the course of the disease has been known for many years. Oosterhuis and Wilde (19) defined that one-third of 150 patients had significant emotional stress before the symptoms of the disease started, and they stated that stress increased the symptoms in 2/3 of the patients. Researchers found that those with the worsening disease had a higher rate of stressful life events than those who were more stable during one-year follow-up. In another study about the effect of psychosocial factors on the clinical course of the disease, conducted by Knieling et al. (20), 42 patients with MG were evaluated. It was found that there was a relationship between psychosocial stress and the emergence of the disease in 35% of the patients. It was observed that those patients, most of whom were found to have depression, were more stable in coping with the disease, and their depressive symptoms decreased after 6 months. In the evaluation after 18 months, no significant correlation was found between demographic data, life stresses, depression and anxiety scores, and the course of the disease (20). In our study, in line with many other studies, two-thirds of our patients identified a stressor factor or life event in the period just before the onset of

disease symptoms. It is known that depression is generally less common in people who can use coping mechanisms effectively and have social support (10). It was noted that in our patients who were evaluated during the interview, depression was not found in patients who could use coping mechanisms in the context of social relationship patterns and personality traits, and their disease symptoms were milder. However, there was no statistical documentation on these observational data.

It has been reported that remission can be achieved in 80% of patients with corticosteroids, the most commonly used immunosuppressant agent in the treatment of MG (21). It was reported that with corticotherapy, remission was achieved at a rate of 30%, detectable improvement was observed at a rate of 45%, and the minimal benefit was achieved at a rate of 15% (22). By evaluating the treatment response, our study determined that 4.1% of our patients had complete remission without medication, 19.4% had remission, 80.6% had minimal symptoms at the last visit, and 42.5% used symptomatic treatment immunosuppressive therapy. In evaluating the change in the clinical situation, 88.8% of our patients recovered and 5.1% exacerbated. At the same time, it was observed that there was no significant change in clinical findings compared to the baseline in 6.1% of the patients.

In our study, in the evaluation of treatment response and the presence of depression, while 7.5% of the patients who achieved 'positive treatment response' including patients with complete remission or remission under treatment, had depression; 27.6% did not have depression, and there was a statistically significant difference between them.

Study Limitations

There were some limitations of our study: The patients with depression were not evaluated according to the medication they were taking and other metabolic factors that might affect the development of depression. In addition, the patients' follow-up neurological examination findings after psychiatric treatment were not evaluated statistically. The low number of more severe patients in group IVa and IVb, lack of grading of depression in patients with depression, and the lack of examination of additional factors other than the presence of depression were reasons for the poor clinical course other limitations of our study. Therefore, we think that further studies are needed on this subject.

Conclusion

This study aimed to draw attention to the importance of evaluating psychiatric disorders that might accompany MG, especially depression, and considering them in planning the treatment. Patients may mistakenly receive a psychiatric diagnosis at the diagnosis stage due to the characteristic clinical features of MG. Further, they may experience secondary depression during the disease due to the adverse effects of the disease. As determined in our study, depression could accompany MG at high rates, MG symptoms could be significantly affected by psychosocial stressors, and the presence of depression in patients might negatively affect the clinical course and treatment response; therefore, the detection and treatment of depression in patients with MG should be considered in terms of the treatment of the disease. Based on the results of our study, we believe that if depression is treated with standard therapy of MG in patients with depression, the clinical course of MG will evolve toward recovery, and chronic exacerbations of the disease will be prevented.

Ethics

Ethics Committee Approval: Study approval was obtained from Ege University Ethics Committee (decision no: 10-5/10, date: 27.05.2010).

Informed Consent: Informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.K., Design: H.K., Data Collection or Processing: F.E.Ç., Analysis or Interpretation: F.E.Ç., Literature Search: F.E.Ç., H.K., Writing: F.E.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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