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Depression and Anxiety Disorders in Patients with Reported Prolactinoma Using Cabergoline Therapy: A Comparative Analysis with Controls

Remisyondaki Prolaktinomalı Hastalarda Kabergolin Tedavisi Altında Depresyon ve Anksiyete Bozuklukları: Kontrol Grubu ile Karşılaştırmalı Bir Analiz

Mustafa Can Şenoymak[1], Nuriye Hale Erbatur[1], Nisa Babacanlar[1], Gizem Yardımcı[2], Ferrat Deniz[1], Arif Yönem[1]

[1]*University of Health Sciences Türkiye, Sultan 2. Abdülhamid Han Training and Research Hospital, Clinic of Endocrinology and Metabolism, İstanbul, Türkiye*

[2]*University of Health Sciences Türkiye, Sultan 2. Abdülhamid Han Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Türkiye*

ABSTRACT

Background: Prolactinoma is the most common functional pituitary tumor. Although effective in reducing prolactin and tumor size, cabergoline can have psychiatric side effects. This study aimed to investigate the prevalence of depression and anxiety disorders in patients with recurrent prolactinoma receiving cabergoline treatment.

Materials and Methods: Patients aged 18 years, diagnosed with prolactinoma and achieving biochemical remission on cabergoline therapy, and the control group were included in the study. The participants completed the Hospital Anxiety and Depression Scale questionnaire. Data collected included the number of years of diagnosis, prolactin levels, cumulative cabergoline dosage, and duration of cabergoline use.

Results: The study included 56 patients with recurrent prolactinoma and 56 controls. The mean age of both groups was 39.4 years [standard deviation (SD)=10.5], with 62.5% female and 37.5% male. The average duration of cabergoline treatment was 40.39 months (SD=30.2). Patients with prolactinoma had a median depression score of 5 [interquartile range (IQR) 2.25-8], whereas the control group had 6 (IQR 4-9). For anxiety, the prolactinoma patients had a median score of 8 (IQR 5-11.75), compared to 7 (IQR 5-9) in the control group. The results revealed no significant difference in depression (p=0.32) and anxiety scores (p=0.19) between the groups. Among the prolactinoma patients, 37.5% (n=21) were found to have symptoms of depression, and 41.1% (n=23) of the control group exhibited symptoms of depression. Anxiety disorders were present in 37.5% (n=21) of the prolactinoma patients and 23.2% (n=13) in the control group. The prevalence of depression and anxiety disorders was not significantly different between the groups (p=0.69 and p=0.1 respectively).

Conclusion: The study found no significant differences in the prevalence of depression and anxiety disorders between patients with recurrent prolactinoma who received cabergoline treatment and the control group. These results suggest that cabergoline dosage and duration do not strongly influence the aforementioned psychiatric comorbidities.

Keywords: Prolactinoma, anxiety disorders, depression, cabergoline

Address for Correspondence: Mustafa Can Şenoymak, University of Health Sciences Türkiye,Sultan 2. Abdülhamid Han Training and Research Hospital, Clinic of Endocrinology and Metabolism, İstanbul, Türkiye

Phone: +90 535 317 89 59 E-mail: senoymak@gmail.com **ORCID ID:** orcid.org/0000-0002-1977-5127

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ÖZ

Amaç: Prolaktinoma, en yaygın fonksiyonel hipofiz tümörüdür. Prolaktin seviyelerini ve tümör boyutunu azaltmada etkili olan kabergolin, psikiyatrik yan etkilere neden olabilir. Bu çalışmanın amacı, remisyondaki prolaktinomalı hastalarda kabergolin tedavisi altındaki depresyon ve anksiyete bozukluklarının yaygınlığını araştırmaktır.

Gereç ve Yöntemler: Çalışmaya, 18 yaş ve üstü, prolaktinoma tanısı almış ve kabergolin tedavisi ile biyokimyasal remisyona ulaşmış hastalar dahil edildi. Katılımcılar, Hastane Anksiyete ve Depresyon Ölçeği anketini doldurdu. Hastaların tanı yılı, prolaktin seviyeleri, kümülatif kabergolin dozu, kabergolin kullanım süresi ve manyetik rezonans bulguları kaydedildi.

Bulgular: Çalışmaya remisyondaki 56 prolaktinoma hastası ve 56 kontrol dahi edildi. Her iki grubun ortalama yaşı 39,4 yıl [standart sapma (SS)=10,5] olup, %62,5'i kadın ve %37,5'i erkekti. Kabergolin tedavisinin ortalama süresi 40,39 ay (SS=30,2) saptandı. Prolaktinoma hastalarının medyan depresyon skoru 5 [çeyrekler açıklığı (IQR) 2,25-8], kontrol grubunun 6 (IQR 4-9) bulundu. Anksiyete için prolaktinoma hastalarının medyan skoru 8 (IQR 5-11,75), kontrol grubunun 7 (IQR 5-9) saptandı. Gruplar arasında depresyon (p=0,32) ve anksiyete skorlarında (p=0,19) anlamlı bir fark bulunmadı. Prolaktinoma hastalarının %37,5'i (n=21) depresyon belirtileri gösterirken, kontrol grubunun %41,1'i (n=23) depresyon belirtileri sergiledi. Anksiyete bozuklukları ise prolaktinoma hastalarının %37,5'inde (n=21) ve kontrol grubunun %23,2'sinde (n=13) mevcuttu. Depresyon ve anksiyete bozukluklarının yaygınlığı gruplar arasında anlamlı farklılık göstermedi (sırasıyla p=0,69 ve p=0,1).

Sonuç: Bu çalışma, remisyondaki prolaktinoma hastaları ile kontrol grubu arasında depresyon ve anksiyete bozukluklarının yaygınlığında anlamlı bir fark olmadığını bulmuştur. Sonuçlar, kabergolin dozajı ve süresinin bu psikiyatrik komorbiditeleri güçlü bir şekilde etkilemediğini göstermektedir.

Anahtar Kelimeler: Prolaktinoma, anksiyete bozuklukları, depresyon, kabergolin

Introduction

Prolactinoma is the most prevalent type of functional pituitary tumor, encompassing 30-60% of all pituitary tumors (1). In contemporary practice, medical therapy, particularly with cabergoline, a dopamine agonist, is the gold standard for treating prolactinoma (2). Cabergoline binds to dopamine receptors, thereby reducing prolactin synthesis and exerting its effects by shrinking the size of the adenoma (3). Although generally well tolerated, cabergoline has certain side effects, including nausea, postural hypotension, heart valve dysfunction, and psychiatric effects (4). Psychiatric side effects of cabergoline include cognitive fog, impulse control disorder, and depression.

Among the psychiatric side effects of cabergoline, impulse control disorder is frequently reported in the medical literature (5,6). However, research on the impact of depression and anxiety disorders remains limited. Depression, a neuropsychiatric disorder characterized by persistent feelings of low mood, anhedonia, and suicidal tendencies, has a lifetime prevalence of 10% (7). Its pathophysiology is believed to involve dopamine and its receptors, with dopamine playing a significant role in emotional regulation, reward, and neurosecretion (8,9). Consequently, alterations in the dopaminergic system, such as changes in dopamine or receptor levels, are associated with depression.

Anxiety, which is typically considered an adaptive response to acute stress, is deemed pathological when functionality is impaired (10). Animal studies have indicated a significant role for dopamine D1 and D2 receptors in anxiety-like behavior models, and dopamine metabolites are also potentially influential in these conditions (11,12).

In this study, we aimed to investigate the prevalence of depression and anxiety disorders among patients with remitted prolactinoma treated with cabergoline and to compare these findings with those of a control group to better understand the impact of cabergoline treatment on mental health outcomes.

Materials and Methods

The study was conducted with the approval of the University of Health Sciences Türkiye, Hamidiye Scientific Research Ethics Committee (approval number: 23/526, date: 22.09.2023) and was conducted in accordance with the Declaration of Helsinki. All participants provided informed consent.

Participants were recruited from the Endocrinology and Metabolism Outpatient Clinic of the University of Health Sciences Türkiye, Sultan Abdülhamid Han Training and Research Hospital between October 2023 and May 2024. Eligible participants were voluntary patients aged 18 years and over who had been diagnosed with prolactinoma and were currently receiving treatment with cabergoline, having achieved biochemical remission.

Patients diagnosed with prolactinoma were included if their prolactin levels were above the normal range, they exhibited an adenoma appearance in the pituitary on magnetic resonance imaging (MRI), and they had no

other conditions causing hyperprolactinemia (such as medication use, polycystic ovary syndrome, kidney or liver insufficiency, etc.). The participants completed the Hospital Anxiety and Depression Scale (HADS) questionnaire. Data collected included years of diagnosis, baseline and current prolactin levels, cumulative cabergoline dosage, duration of cabergoline use, MRI findings, demographic characteristics, and comorbidities.

The exclusion criteria were as follows: patients under 18 years old, those with macroprolactinemia, pregnant or breastfeeding women, individuals with hypothyroidism, polycystic ovary syndrome, advanced liver or kidney insufficiency, patients diagnosed with depression, anxiety disorders, schizophrenia, or parkinsonism, and those taking medications that could affect prolactin levels or alter questionnaire scores (e.g., glucocorticoids, oral contraceptives, antidepressants, antipsychotics, L-dopa). Patients for whom data were inaccessible through the system were also excluded. Control group participants were individuals without known diseases of similar age and gender who presented to the outpatient clinic for routine examinations.

The Hospital Anxiety and Depression Scale

The HADS was developed by Zigmond and Snaith (13) in 1983, and its Turkish validity study was conducted by Aydemir and Köroğlu (14). A total of 14 questions were included, seven of which measured anxiety and the other seven measured depression. Each question contained four items, and patients were asked to mark the item that best fit their condition. The cutoff score for the seven-item depression subscale was 8, while that for the anxiety subscale was 10 (14,15).

Statistical Analyses

Statistical analyses were performed using SPSS version 25 (IBM Corporation, Armonk, NY, USA). Descriptive statistics [mean ± standard deviation (SD) for continuous variables, frequencies and percentages for categorical variables] were used to summarize the baseline characteristics of the participants. Comparisons between the control and disease groups were conducted using (Mann-Whitney U for continuous variables, chi-squared tests for categorical variables). $p<0.05$ was considered statistically significant.

Results

The study comprised 56 patients with remitted prolactinoma who were on cabergoline treatment and 56 control participants without known diseases who were matched for age and gender and presented for routine examinations. The mean age of both groups was 39.4 years (SD=10.5), with 62.5% female and 37.5% male in each group. The mean baseline prolactin level of the patients was 30.31 ng/mL (SD=63.12). The cumulative cabergoline dose used by the patients was 105.25 mg (SD=108.58). The average duration of cabergoline treatment among patients with prolactinoma was 40.39 months (SD=30.2). Table 1 shows the demographic and clinical profiles of the two groups.

Among the prolactinoma patients, 37.5% (n=21) were diagnosed with depression according to the HADS. Moreover, 41.1% (n=23) of the control group exhibited symptoms of depression. Anxiety disorders, as measured by The HADS, were present in 37.5% (n=21) of the prolactinoma patients and 23.2% (n=13) in the control group (Table 2).

The chi-square test of independence was used to investigate the association between prolactinoma status and the presence of depression. The results indicated no significant association between prolactinoma status and depression (p=0.69) suggesting that the prevalence of depression was not significantly different between patients with recurrent prolactinoma and the control group. Additionally, the chi-squared test of independence indicated

Table 1. Demographics and clinical profiles of the study participants

Characteristic	Prolactinoma patients (n=56)	Control group (n=56)
Mean age (years)	39.4±10.5	39.4±10.5
Female, n (%)	35 (62.5%)	35 (62.5%)
Males, n (%)	21 (37.5%)	21 (37.5%)

Mean ± standard deviation for continuous variables and frequencies and percentages for categorical variables were used to summarize the baseline characteristics of the participants

Table 2. Prevalence of depression and anxiety in participants

Condition	Prolactinoma patients (n=56)	Control group (n=56)	p-value
Depression, n (%)	21 (37.5%)	23 (41.1%)	0.69
Anxiety, n (%)	21 (37.5%)	13 (23.2%)	0.1

Comparisons between the control and disease groups were conducted using Mann-Whitney U for continuous variables

no significant association between prolactinoma status and anxiety (p=0.1), suggesting similar anxiety prevalence in both groups (Table 2). Prolactinoma patients had a median depression score of 5 [interquartile range (IQR) 2.25-8], whereas the control group had a median score of 6 (IQR 4-9). For anxiety, the prolactinoma patients had a median score of 8 (IQR 5-11.75), whereas the control group had a median score of 7 (IQR 5-9) in the control group. A Mann-Whitney U test was used to compare depression and anxiety scores between the two groups. The results showed no significant difference in the depression (p=0.32) and anxiety scores (p=0.19) between the prolactinoma and control groups, indicating similar levels of depression and anxiety.

Discussion

The prevalence of psychiatric side effects, particularly impulse control disorder, associated with cabergoline therapy for prolactinoma has been documented in the medical literature (5,6). However, our study aimed to delve deeper into less explored areas, specifically depression and anxiety disorders, in patients with recurrent prolactinoma undergoing cabergoline treatment. Understanding the prevalence and potential contributing factors of these psychiatric conditions is crucial for comprehensive patient care and treatment management. We examined the frequency of these disorders with that of a healthy population to explore potential cabergoline-related side effects. Our findings revealed no significant differences in anxiety disorders and depression between patients with recurrent prolactinoma who received cabergoline therapy and the control group. This study is the first to investigate the relationship between cabergoline dosage/duration and depression or anxiety disorders in patients with prolactinoma.

Although studies have reported conflicting results, depression and anxiety disorders are frequently observed in patients with prolactinoma (16-19). This occurrence can be linked to several factors, including the chronic nature of prolactinoma, long-term medication use, and hypogonadism. In our study, the similarity in anxiety and depression scores between patients with prolactinoma who achieved biochemical remission and the general population indicated that the neuropsychiatric effects of the disease could improve with treatment. In a study by Buckman and Kelner (20), it was reported that patients successfully treated with bromocriptine experienced a decrease in anxiety and depression scores. Similarly, some studies have reported an increase in quality of life in prolactinoma patients receiving medical treatment (18). However, the findings of our study may have been influenced by the high prevalence of psychiatric disorders in the control group. In Türkiye, it is reported that 18% of the population experiences a mental disorder at some point in their lives, with the prevalence of depression ranging from 4% to 9%. Globally, it is reported to be around 15%. However, in our study, the prevalence of depression was reported to be remarkably high at 41%, which may obscure the depressive condition of patients with prolactinoma treated with cabergoline (21).

Cabergoline acts on dopamine D2 receptors, and understanding the complex realm of dopamine D2 receptors is necessary for comprehending the neuropsychiatric side effects of cabergoline. D2 receptors serve as the primary modulators of dopaminergic activity, operating through various mechanisms to fulfill this role. This pathway is particularly closely associated with reward systems, mood disorders, and motivation (22-24). D2 autoreceptor suppress dopaminergic neuron activation and inhibit dopamine secretion. Consequently, it has been hypothesized that alterations in dopamine levels or receptor sensitivity associated with D2 receptors could potentially be linked to depression and anxiety disorders (22,23). Cabergoline may induce these alterations and disrupt the delicate balance of neurotransmitter signaling, predisposing individuals to mood dysregulation and anxiety.

On the other hand, some studies have indicated the potential anxiolytic and antidepressant effects of cabergoline. In a study by Anokhin et al. (25), rats administered cabergoline showed an increase in brain-derived neurotrophic factor (BDNF) mRNA expression in the midbrain, suggesting possible anxiolytic effects. Furthermore, evidence from a study by Chiba et al. (26) confirmed the antidepressant effects of cabergoline in rats. It has been noted that the underlying mechanism involves increased levels of BDNF in the hippocampus, which is typically low in depression. In summary, results from studies examining the relationship between cabergoline and depression/anxiety disorders are conflicting, emphasizing the need for further evidence to elucidate this relationship. In parallel with these outcomes, our study did not find a relationship between the duration of cabergoline use, its cumulative dose, and elevated anxiety and depression scores.

This study addresses a significant gap in the literature by focusing on the prevalence of depression and anxiety disorders in patients with recurrent prolactinoma undergoing cabergoline treatment. By delving into these often-understudied psychiatric effects, this research provides valuable insights into the holistic management of prolactinoma patients. One of the strengths of our study lies in its inclusion of a control group, allowing for a comparative analysis of psychiatric symptomatology between patients with prolactinoma and individuals without known diseases

along with the long-term follow-up of patients and the inclusion of both genders in the study.

Study Limitations

It is important to acknowledge the limitations inherent to this study. First, the limited sample size may have limited the generalizability of the findings. Furthermore, the study did not comprehensively investigate other comorbidities or socioeconomic factors that could potentially contribute to depression and anxiety disorders. Additionally, the recruitment of participants from a single outpatient clinic may introduce selection bias, further limiting the generalizability of the results to other populations.

Conclusion

The present study investigated the prevalence of depression and anxiety disorders in patients with recurrent prolactinoma undergoing cabergoline treatment. Despite known psychiatric side effects of cabergoline, we found no significant differences in these disorders compared with the control group. This suggests that cabergoline dosage/duration does not strongly influence these psychiatric comorbidities in this population. However, the complex modulation of dopamine D2 receptors and conflicting evidence from preclinical studies warrant further investigation.

Ethics

Ethics Committee Approval: The study was conducted with the approval of the University of Health Sciences Türkiye, Hamidiye Scientific Research Ethics Committee (approval number: 23/526, date: 22.09.2023).

Informed Consent: All participants provided informed consent.

Authorship Contributions

Concept: M.C.Ş., N.H.E., F.D., A.Y., Design: M.C.Ş., N.H.E., F.D., A.Y., Data Collection or Processing: M.C.Ş., N.B., G.Y., Analysis or Interpretation: N.H.E., N.B., G.Y., F.D., A.Y., Literature Search: M.C.Ş., N.B., G.Y., F.D., A.Y., Writing: M.C.Ş., N.H.E., N.B., G.Y.,

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