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Behavioral Changes Associated with Dopamine Agonist Treatment in the Follow-up of Restless Legs Syndrome: A Retrospective Study

Huzursuz Bacaklar Sendromunda Dopamin Agonisti Tedavisi ile İlişkili Davranış Değişiklikleri: Retrospektif Bir Çalışma

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ABSTRACT Objective: Restless legs syndrome (RLS) is a neurological sensorimotor disease. Behavioral changes are little-known concern during the treatment and follow-up of RLS. The aim of the study is to highlight the behavioral changes associated with dopamine agonist treatment in the follow-up of RLS, such as dopamine dysregulation syndrome (DDS) and impulse control disorder (ICD). **Material and Methods:** We analyzed clinical data from RLS patients' files from the previous 15 years retrospectively. The patients receiving dopaminergic monotherapy for RLS, who came to follow-up on a regular basis and whose last examination was within the last 6 months were chosen. The average age of patients without behavioral changes was 48.60±9.21 years. **Results:** Of the patients' complaints, legs were affected in 90.90%, arms and legs together were affected in 9.09%. Dopamine agonist-related changes were observed in 6 female patients. Mean age of these patients was 40.16±9.23 years old. They showed behavioral abnormalities such as uncontrolled drug use, shopping curiosity, hypersexuality, smoking, and space decoration. One patient presented with manic episode together with DDS. The average age of RLS patients who experienced behavioral changes was younger. Average dose at which behavior changes were observed was unclear since 4 of 6 patients with behavioral changes developed DDS. Despite using a regular-low dose agonist, the other two female patients showed ICD without DDS. **Conclusion:** With dopaminergic treatment, behavioral changes that may cause problems in family and social life can develop. When prescribing dopaminergic medications, it is important to ask if the patient has any behavioral changes and pay close attention in a busy polyclinic.

Keywords: Restless legs syndrome; dopamine dysregulation syndrome; impulse control disorder; punding; dopamine agonist

ÖZET Amaç: Huzursuz bacaklar sendromu (HBS) nörolojik bir sensörimotor hastalıktır. HBS'nin tedavi ve takibi sırasında ortaya çıkabilen davranış değişiklikleri yaygın değildir. Çalışmamızın amacı, HBS'nin takibinde dopamin agonisti tedavisi ile ilişkili dopamin disregülasyonu sendromu (DDS) ve dürtü kontrol bozukluğu (DKB) gibi davranış değişikliklerine dikkat çekmektir. **Gereç ve Yöntemler:** HBS tanısı olan hastaların dosya kayıtları geriye dönük olarak 15 yılı içine alacak şekilde incelendi. HBS için tek tip dopaminerjik tedavi kullanan, düzenli olarak kontrole gelen ve son kontrol muayenesi 6 ay içinde yapılmış olan hastalar seçildi. Davranış değişikliği olmayan hastaların ortalama yaşı 48,60±9,21 yıldı. **Bulgular:** Hastaların şikâyetlerinin %90,90'ı bacaklar, %9,09'u da kol ve bacaklar birlikte etkilenmiş olarak kaydedilmişti. Altı kadın hastada dopamin agonistleri ile ilişkili davranış değişiklikleri vardı. Bu hastaların ortalama yaşı 40,16±9,23 idi. Bu hastalar kontrol edemedikleri bağımlılık şeklinde yüksek doz ilaç kullanımı, aşırı alışveriş, cinsel yaşamda artış, kontrol edemedikleri sigara kullanımı, amaçsız ortam dekorasyonları şeklinde davranış değişiklikleri göstermişti. Bir hasta DDS ile beraber manik atağı tanısı almıştı. Davranış değişiklikleri yaşayan HBS hastalarının ortalama yaşı daha gençti. Davranış değişikliklerinin gözlendiği ortalama ilaç dozu, davranış değişiklikleri olan 6 hastanın 4'ünde DDS geliştiği için belirsizdi. Diğer 2 hasta düzenli-düşük doz bir agonist kullanmasına rağmen DKB gösterdi. **Sonuç:** Dopaminerjik tedavi ile aile ve sosyal yaşamda sorunlara neden olabilecek davranış değişiklikleri gelişebilir. Dopaminerjik ilaçlar reçete edilirken, yoğun poliklinik şartlarında dikkatli olunmalı ve hastanın herhangi bir davranış değişikliği olup olmadığı iyi sorgulanmalıdır.

Anahtar Kelimeler: Huzursuz bacaklar sendromu; dopamin disregülasyonu sendromu; dürtü kontrol bozukluğu; punding; dopamin agonisti

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Restless legs syndrome (RLS) is distinguished with an uncontrollable urge to move, primarily the legs, and is characterized by uneasiness during immobility, prompting a desire to move the legs to alleviate the discomfort. Arms may be less often involved into the complaints. Symptoms usually peak in the evening or at night, and they may make it difficult to sleep. Related complaints can sometimes spread to the daytime.[1,2] The intensity and frequency of RLS symptoms determine the treatment for primary RLS. It may be treated with lifestyle changes, whereas RLS usually necessitates the use of drugs. Dopaminergic medications are the most consistently effective treatments for RLS symptom relief.[1-3]

Dopamine is an important neurotransmitter for a variety of brain functions, including motor regulation, motivation, reinforcement learning, and reward. There are three major dopaminergic pathways in the central nervous system: (i) the nigrostriatal pathway, which is involved in motor function; (ii) the mesocorticolimbic pathway (also known as the reward system), which is involved in reward- and aversion-related cognition, as well as executive functions (iii) the tuberoinfundibular pathway, which influences hormone secretion, including prolactin. Various conditions such as Parkinson's disease, compulsive repetition of rewarding behaviors [as in addictive disorders and impulse control disorders (ICD)], drug addiction, and certain endocrine disorders such as prolactinoma may be caused by dysfunction of these different pathways. They can also be affected when dopamine replacement therapy (DRT) is used to treat such diseases.[4-12] Changes in dopamine function physiologically as an error-prediction and teaching signal, activating specific parts of dopamine receptors, which leads to changes from purpose-driven behaviors to habituation, or persistent neuronal activation that actuates behavior sensitization are some of the mechanisms by which dopaminergic agents may influence these pathways.[9-12] And in relation to these, dopaminergic drugs have been linked to possible neuropsychiatric side effects, especially in Parkinson's disease. It is well recognized that during DRT, Parkinson's patients experience a variety of behavioral problems on the impulsive-compulsive spectrum.[5,9-12] It first gained notice as a clinical picture linked to dopaminergic therapy in Parkinson's patients. Due to the hedonic influence of dopaminergic agents and elevated mood, certain patients continued to increase the dosage and frequency of dopaminergic drugs despite physician alerts. The clinical picture was compared to a behavioral tendency seen in drug abusers who develop a habit of regularly taking similar substances to avoid withdrawal symptoms, known as "hedonistic homeostatic dysregulation".[13,14] This condition is referred to as dopamine dysregulation syndrome (DDS) because it is a side effect of dopaminergic therapy in Parkinson's disease patients.[5,15,16] During DRT, impulsive behavioral disorders in Parkinson's patients are usually divided into three categories: "ICD" which is linked to reward-seeking behaviors; "punding", which is a term used to describe complex, prolonged, stereotyped behavior; and "DDS" which is a reward system dysfunction linked to self-control issues such as impulsivity including drug abuse, gambling, or sexual behavior.[14-16]

These behavioral disorders are not limited to Parkinson's disease patients. In the follow-up of RLS, DDS and ICD associated with dopaminergic treatment are less well-known disorders than Parkinson's disease. In recent years, it has received greater attention.[6-8] And, based on our own RLS experiences, we would like to call attention to the behavioural changes associated with dopamine agonist treatment in the management of RLS.

MATERIAL AND METHODS

This research was carried out retrospectively by scanning the file records of patients who had been diagnosed with primary RLS for the previous fifteen years. Our study was approved by the "Retrospective Study Information Form" dated 26.04.2021 and numbered "E-62977267-000-6345" at Haydarpaşa Numune Training and Research Hospital, in accordance with the Helsinki Declaration Principles. Only patients whose RLS diagnosis code was entered as a single diagnosis were registered in the computer records. The diagnosis of RLS is made in our neurology movement disorders outpatient clinics using the international RLS research group diagnostic criteria.

Patients with restless legs syndrome who have changed their behavior were chosen during this period. Behavioral changes have been identified in 6 female RLS patients over the past 15 years, and these behavioral changes occurred when the patients were undergoing dopamine agonist monotherapy. After being diagnosed with RLS, however, dopaminergic medication was administered to 150 patients in total. Patients with primary RLS who had routine follow-up visits and were only taking dopamine agonist monotherapy were included in the study. The study excluded patients who had not had a control examination in the previous 6 months. Only patients receiving dopaminergic monotherapy for RLS, who came to follow-up on a regular basis and whose last examination was within the last 6 months were chosen (44 patient). In addition to the demographic characteristics of these 44 RLS patients without behavioral changes, the clinical follow-up data of 6 RLS patients with behavioral changes associated with dopamine agonist treatment were documented.

STATISTICAL ANALYSIS

SPSS (Statistical Package for the Social Sciences) for Windows 13 was used to prepare the statistical analysis. The data from the analysis was evaluated using descriptive statistical methods (mean, standard deviation, frequency, percentage, minimum, maximum).

RESULTS

In the study, there were 44 patients with primary RLS (3 males and 41 females) who had a follow-up visit during the previous 6 months and were on dopamine agonist monotherapy. Six patients had behavioral changes as a result of dopamine agonist therapy.

The patients without behavioral changes who were first examined had an average age of 48.60±9.21 (36-67) years. At the time of the outpatient clinic's first admission, the average length of RLS-related problems was 4.20±2.10 years. RLS-related complaints were only recorded in the legs in 40 patients (90.90%), and in both arms and legs in 4 patients (9.09%) (Table 1). The patients were on monotherapy with a dopamine agonist (pramipexole or ropinirole).

Six patients (12%) were observed to have behavioral changes as a result of dopamine agonist therapy for RLS. They were 40.16±9.23 years old. Before starting dopamine agonist treatment, the average duration of RLS-related complaints was 5.66±5.27 years. After an average of 5.83±3.25 months on the dopamine agonist, the patients showed behavioral changes.

The average age of RLS patients who experienced behavioral changes was younger than the patients without behavioral changes. These 6 patients, all of whom were female, were taking pramipexole. The clinical follow-up results for these 6 RLS patients with behavioral changes are described below.

CASE 1

The patient is a 32-year-old married housewife. The patient's RLS symptoms occurred only at night, when she was lying in bed, for 3 years. She felt compelled to move her legs. She did not smoke, drink, or use any other drug. She had been taking amitriptyline 25 mg/day for fibromyalgia for a year. Dopamine agonist (0.250 mg/evening) was administered after RLS was diagnosed. Her problems were completely addressed by the end of the first month (0.5 mg/evening). Four months later, the patient's husband claimed that she

TABLE 1: Patient demographics.

	Without BC-RLS (n=44)	With BC-RLS (n=6)	Total n=50
Age	48.60±9.21	40.16±9.23	p=0.03
*Localization: legs	40 (90.90%)	6 (100%)	
*Localization: legs+arms	4 (9.09%)	-	
**Time	-	5.83±3.25	

*Localization: Where RLS-related complaints occur; **Time: After dopamine agonist treatment, the time in months on average when the behavioral changes begin; BC: Behavioral changes; RLS: Restless leg syndrome.

had spent too much money and had a compulsive shopping tendency, and that she had exceeded their budgets with excessive purchases. The patient was prone to polygamy. It was discovered that she was using high doses of medications regardless of the prescribed dose. We advised the patient and her family to stop taking dopaminergic medications and seek psychiatric help. Our patient, on the other hand, declined to stop taking the dopamine agonist and come in for the follow-up exams. She was brought to us by her mother 2 years later. The patient was deafeningly silent and showed signs of malnutrition. Via extensive examinations and psychiatric consultations, she was diagnosed with major depression. The patient was admitted to the psychiatry clinic for follow-up.

CASE 2

When she was first examined, a 45-year-old married woman who worked as a medical staff had complained of restless legs for 5-6 years. RLS-related symptoms in the patient began at night as leg pain while the patient was sleeping, and the patient's complaints lessened as the patient walked. After 3-4 years, complaints began to manifest themselves as feelings of unease during the daytime rest period. She smoked 4-5 times a day and did not drink or use any other substances. There was no underlying illness or treatment. After being diagnosed with RLS, she was prescribed a dopamine agonist (0.250 mg/evening), which fully alleviated her symptoms in just 1 week. She did not come back for daily checks afterwards. She confessed to taking extra dopamine agonist doses because she tried to be well a year after starting dopamine agonist therapy. Since the total dose changed regularly, she could not mention a precise dose. She started by renovating her home, adjusting the layout in the event of frequent moves, and then she moved on to repeating decoration arrangements in the clinic where she worked. Apart from the rise in her libido, her inability to sleep was noticed. When she was brought to our clinic, dopamine agonists were stopped. Within a month, the patient was able to resume her usual everyday activities. Gabapentin was prescribed due to a rise in RLS symptoms. Gabapentin 800 mg/evening helped her feel better.

CASE 3

The patient's symptoms began 10 years ago in the evenings, with leg pain and an urge to move them. The patient's symptoms have worsened in the last 4-5 years, and she now feels discomfort and restlessness throughout the day. Dopamine agonist (0.250 mg/evening) was started after the diagnosis of RLS. During the first- and third-month's follow-up examinations, the patient made no complaints. After 6 months, the woman began to raise the medication dosage without consulting the doctor, claiming that her symptoms had worsened. It is unclear at what dose and frequency the patient used a dopamine agonist. She also failed to attend routine follow-ups. She began smoking (2 packs/a day) despite never having smoked before. Making uncontrollable purchases; she had incurred credit card bills that exceeded their budgets. The patient refused to come to the controls by herself. The patient's relatives had come to ask for assistance. We requested that she discontinue her dopaminergic treatment. However, the patient could not be persuaded and declined to change her treatment. During the family interview, it was revealed that she had access to medications at various health centers and, sadly, did not follow any other recommendations.

CASE 4

During the first examination, a 28-year-old female and single patient employed as a manager in the private sector. She had complained of restless legs for three years in the legs. She never smoked a cigarette, drank alcohol, or used some other drug. There was no underlying illness or treatment. Dopamine agonist therapy (0.250 mg/evening) was initiated due to RLS. As soon as she began dopamine agonist therapy, the patient felt better. We heard from her family 6 months later that the woman had been admitted to a psychiatric facility with a diagnosis of acute manic episode. Upon interacting with him at the psychiatry clinic, we learned that the patient had been using an uncontrolled dopamine agonist for the previous three months. Her family confirmed that she had been uncontrollably obtaining dopamine agonist for the previous three months. She had taken the drug where needed (dose unknown) when she complained that her pain had worsened. The dopamine agonist ther-

apy was discontinued, and the patient was referred to a psychiatry clinic for further evaluation.

CASE 5

She was a married housewife of 46 years old. Five years before she applied to us, she had complaints of restlessness in the legs at night and the urge to move. She did not use alcohol or any other drug while smoking one pack of cigarettes a day. Therapy with a dopamine agonist (0.250 mg/evening) was initiated. The patient's symptoms were completely relieved by dopamine agonist (0.250 mg/evening). There were no complaints during the first- and third-month follow-ups. Although the patient continued to take the medication daily (0.250 mg/evening), she developed an insatiable desire to shop after the 6th month. Credit card loans incompatible with her income status arose as a result of transactions that could not be avoided. The patient came to the control at her own request, and one month after ceasing dopaminergic therapy, she was completely back to her usual everyday activities. For her RLS-related symptoms, gabapentin treatment (400 mg/evening) was prescribed, and she was relieved.

CASE 6

A married housewife of 37 years old. The symptoms began 3-4 years before she came to our clinic in the form of nighttime restlessness in the legs. The patient had an intense, frequently irresistible desire to move her legs, which was generally followed by physical discomfort. Physical exercise, such as walking or stretching, helped to alleviate her symptoms to some extent. She only smoked a couple of cigarettes and drank a couple of glasses of wine on special occasions. She did not take any other drugs. The patient's symptoms were totally relieved after starting a dopamine agonist for RLS (0.5 mg/evening). She raised the number of cigarettes smoked in the 4th month while using the drug regularly daily dosage (0.5 mg/evening), consuming more than 2 packs of cigarettes a day by smoking impulsively. When the patient was brought to the control at the request of her family, dopamine agonist treatment was terminated despite the fact that she was not disturbed by this condition. The patient's dopamine agonist medication was stopped. The number of cigarettes smoked decreased, but the smoking habit persisted. The patient claimed that she enjoyed smoking and did not want to stop. Gabapentin 600 mg twice a day relieved RLS-related symptom.

DISCUSSION

There are inadequate data samples in the literature about behavioral changes associated with follow-up of RLS patients on dopamine agonist therapy.[17] Patients taking dopaminergic treatment for RLS had a 7 percent pathological gambling rate, while hypersexuality had an 8 percent, punding had a 10%, and compulsive eating had a 23% rate.[6] At low doses, no difference in ICD was found between patients receiving and not receiving agonists in another prospective study.[7] Impulse control behaviors were stated to be 7.1 percent in another study that questioned the prevalence of impulse control behaviors in RLS.[8]

We observed that dopamine agonist monotherapy caused behavioral changes in 12% of our primary RLS patients. The patients with behavioral changes were younger on average, and they had been experiencing related complaints for a longer period of time. At a mean of 5.83±3.25 months after the start of the dopamine agonist treatment, the patients showed behavioral changes. Due to DDS, the dose was uncertain in four of our patients, but it was estimated to be high. Interestingly, behavioral changes were observed in 2 of our patients while they were receiving regular low-dose therapy. This finding is important because behavioral changes with low-dose dopamine agonist therapy are not widely known. While our data show a 12 percent change in behavior, we believe this figure does not represent the true rate, and this is a study limitation. The reasons for this negative viewpoint can be articulated in a few ways. To begin, we gathered patients who were on dopamine agonist monotherapy, were routinely followed up on, and whose clinical status was examined within the last 6 months in order to build a homogeneous patient group (n=44). Also, in addition to those who received combination therapy, patients did not visit our clinic for a follow-up examination were also excluded from the study. As a result, despite being treated with a dopamine agonist, these patients were omitted from the study and their numerical values were not in-

cluded. In fact, our study only shows the findings of 50 RLS patients (6 patients with behavior changes and 44 patients without behavior changes) using dopamine agonists, and this does not reflect the fate of all our patients with RLS. All of our patients with RLS did not come for a regular follow-up examination and therefore we did not know the fate of all of them. After their symptoms had been relieved by treatment, our RLS patients tended not to return for follow-up exams unless there was a serious issue. Instead, they tended to go to places where drugs were more easily available and obtained the prescription. While the number of patients receiving dopaminergic treatment in the outpatient clinic was actually higher, we presented the course of fifty dopamine agonist monotherapy prescriptions, following them regularly.

CONCLUSION

Over a fifteen-year period, abnormal behavior was observed in 6 RLS patients treated with dopamine agonist therapy. Cases 1, 2, 3 and 4 displayed behavioral abnormalities in addition to DDS, such as uncontrolled medication abuse, while Cases 5 and 6 showed behavioral abnormalities with low daily treatment doses. When these clinical conditions that may have developed during the treatment of RLS with dopamine agonists escaped attention, they might cause a significant problem in family and social life, and we were only informed at this stage. As a result of these encounters, when patients seek agonist prescriptions in a busy polyclinic, a great deal of attention must be paid. Furthermore, not only in neurology outpatient clinics, but also in other internal branches such as endocrinology, this issue should be considered. Behavioral changes should be questioned when administering dopaminergic medications.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Figen Varlıbaş;* ***Design:*** *Figen Varlıbaş, Gülbin Yüksel, Özkan Akhan, Zeynep Baştuğ Gül, Burçak Ergin;* ***Control/Supervision:*** *Figen Varlıbaş, Gülbin Yüksel;* ***Data Collection and/or Processing:*** *Figen Varlıbaş, Gülbin Yüksel, Özkan Akhan, Zeynep Baştuğ Gül, Burçak Ergin;* ***Analysis and/or Interpretation:*** *Figen Varlıbaş, Gülbin Yüksel;* ***Literature Review:*** *Figen Varlıbaş, Gülbin Yüksel, Özkan Akhan, Burçak Ergin, Zeynep Baştuğ Gül;* ***Writing the Article:*** *Figen Varlıbaş, Burçak Ergin, Zeynep Baştuğ Gül;* ***Critical Review:*** *Figen Varlıbaş, Canan Eyi.*

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