Hypersexuality Complication of Dopamine Agonists: Pramipexole or Ropinirole?
Dopamin Agonistlerinin Hiperseksüalite Komplikasyonu; Pramipeksol Mü? Ropinirol Mü?

Abstract

Antiparkinsonian drugs especially dopamine agonists have many side effects. Dopamine agonists have been linked with compulsive inappropriate behaviours such as gambling, compulsive shopping, hobbyism, other repetitive or purposeless behaviours such as punding, compulsive eating and hypersexuality. However pathological hypersexuality has rarely surfaced in routine Parkinson's disease practice. We present clinical findings of a seventy-three year old male Parkinson's disease patient with diagnosis of hypersexuality as a side effect of pramipexole. After pramipexole was withdrawn, dopamine agonist was changed to ropinirole and full remission was observed. Prevalence of psychiatric disorders in patients suffering from Parkinson's disease varies from 12 to 90%. Hypersexuality is a common impulse control disorder seen in Parkinson's disease and noted in these patients taking a variety of dopaminergic agents; including levodopa, dopamine agonists or MAO inhibitors. In our patient, pramipexole caused hypersexuality unexpectedly. Since this case constitutes interesting findings in two different points, one is hypersexuality with pramipexole, the other is no hypersexuality with use of ropinirole after pramipexole withdrawal, it is chosen to be presented here.

Keywords: Parkinson's disease, pramipexole, ropinirole, hypersexuality, impuls control disorder

Özet

Antiparkinson ilaçları, özellikle dopamin agonistleri birçok yan etkiye sahiptir. Dopamin agonistleri kompulsif uygunsuz davranışlar ile ilişkilendirilir. Bunlar; kumar bağımlılığı, kompulsif alışveriş, hobiler, punding, kompulsif yeme, hiperseksülaite gibi diğer tekrarlayıcı davranışlardır. Bununla birlikte patolojik hiperseksüalite, rutin Parkinson hastalığı pratiğinde nadiren ortaya çıkmıştır. Burada 73 yaşında Parkinson Hastalığı olan ve Pamipeksol yan etkisi olarak hiperseksüalite geliştiren hastamızı sunuyoruz. Pramipeksol kesildikten sonra, tedavisi ropinirol ile değiştirilen hastada tam düzelme gözlenmiştir. Parkinson hastalarında psikiyatrik bozukluk görülme prevelansı %12-90 arasında değişmektedir. Hiperseksüalite, Parkinson hastalığında görülen yaygın bir dürtü kontrol bozukluğudur ve Levodopa, dopamin agonisti veya MAO inhibitörü gibi dopaminerjik ilaç alan hastalarda görülür. Hastamızda pramipeksol beklenmedik şekilde hiperseksüaliteye neden olmuştur. Bu olgu; biri pramipeksol ile oluşan hiperseksüalite, diğeri pramipeksol kesildikten sonra ropinirol kullanımıyla düzelen bulgular olmak üzere iki farklı noktada ilginç bulgular oluşturduğundan, burada sunulmak üzere seçilmiştir.

Anahtar Kelimeler: Parkinson Hastalığı, pramipeksol, ropinirol, hiperseksüalite, dürtü kontrol bozukluğu

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INTRODUCTION

Compulsive and addictive behaviours of patients with Parkinson's disease (PD) are now well known. The first hypersexuality case series were reported by Uitti et al. in 1989 with antiparkinsonian treatment (1). Other studies had reported many kinds of compulsive and addictive behaviours such as mania, pathological gambling, binge eating, zoophilia, transvestic fetishism, and obsessive-compulsive disorders (2).

In PD treatment, antiparkinsonian drugs have many side effects on patients, especially dopamine agonists. Dopamine agonists have been linked with compulsive inappropriate behaviours such as gambling, compulsive shopping, hobbyism, other repetitive or purposeless behaviours such as punding, compulsive eating and hypersexuality. The compulsive behaviours appear to be most common in men with young-onset PD (3). However pathological hypersexuality has rarely surfaced in routine PD practice (4).

Pathological hypersexuality has been defined as "the need for sexual behaviours that consume so much money, time, concentration and energy which results in the patient getting out of control. Unwanted paraphiliac thoughts prevent concentration on other life demands, are the source of anxiety and orgasm does not produce satiety in the way it typically does for age-mates" (5).

Pramipexole, like other dopamine agonists used for treating PD, might induce psychotic symptoms due to central dopaminergic stimulation. A published meta-analysis demonstrated that, relative to placebo, pramipexole increased the risk of hallucinations (6).

This report focuses on the hypersexuality of a 73-year-old male patient developed after the use of pramipexole for treatment of his PD.

CASE REPORT

The seventy-three-year-old male patient's first complaint was a tremor on his right hand. Eight months after his first doctor visit, he was referred to our hospital's Neurology department-Movement disorders outpatient clinic with a possible PD diagnosis. He was examined and diagnosed with PD in our outpatient clinic. In his neurological examination, there was an absence of associated movements with severe resting tremors on the right side.

Palmomental reflexes were bilaterally positive. Moderate bradykinesia was observed during examination. The patient was on antiparkinsonian treatment at the time of examination. On his cranial MRI, tiny hyperintensity changes on T2 weighted images in bilateral frontoparietal subcortical and left peritrigonal deep white matter were observed. His laboratory tests, including liver, kidney, thyroid function tests, electrolytes, blood glucose level and haematological parameters were all normal except vitamin B12 level (which was lower than normal values). He got vitamin B12 replacement parenterally. He was getting Levodopa + Carbidopa + Entacapone (100/25/200 mg) preparation four times a day, acetylsalicylic acid 150 mg once a day, and antihypertensive therapy.

The tremor was very disabling for the patient. Dopamine agonist has been decided to begin under close control. He had no psychiatric history or any drug complications up to now. He had no cardiopulmonary disease except hypertension. Pramipexole was started at 0.75 mg /day initially and in two weeks raised to 1.5 mg/day (in divided doses three times a day). After one month's period from pramipexole onset, he began to suffer from increased sexual activity. The patient started to bring up his extreme sexual desire. He mentioned that he requested his wife to have sexual intercourse several times a day. He also made rude and sexually explicit jokes to his granddaughters. He also tried to stroll

in the house naked when lights were on and curtains were open. Moreover, he also started to masturbate, an activity he had never done for many years under unacceptable circumstances such as when lights were on and curtains were open.

After these hypersexuality problems had started, his daughter took him to be checked in our patient clinic again. He was examined physically and neurologically. There was no objective change in neurological examination, tremor was less than before, even no bradykinesia was observed. Physical examination was also normal. Pramipexole was withdrawn and replaced with ropinirole (8 mg/day).

Once pramipexole was withdrawn and replaced with ropinirole, complete remission about the increased sexual activity was observed and the patient returned to his normal sexual behaviour. No hypersexuality was observed during the use of ropinirole. In neurological examination, no difference was determined between the two preparations (pramipexole and ropinirole).

DISCUSSION

Pramipexole is a non-ergot synthetic aminobenzathiazol derivative. It is a nearly pure dopamine agonist (DA) with high selectivity for the D2-like family dopamine receptor class including D2, D3, D4 receptors. Pramipexole has a five to seven times greater affinity for the D3 receptor subtype with lower affinities for the D2 and D4 receptor subtypes (7). Impulse control disorders (ICD) by pramipexole use have been reported, and this effect is generally associated with selective D3 stimulation (8). Other frequently used dopamine agonist ropinirole has the highest affinity for D2, and then for D3 and D4 receptors (8).

The prevalence of psychiatric disorders in patients with Parkinson's disease varies from 12 to 90 %. The most common disorder in the natural evolution of Parkinson's disease is depression. Episodes of psychosis and hypomania are related to treatment with levodopa (LD) and dopaminergic agents (9).

Addictive disorders may occur in PD, either typical substance-related addictions that are known as dopamine dysregulation syndrome (DDS) or behavioural addictive syndromes usually presenting as ICDs that include pathological gambling, hypersexuality, compulsive eating and buying (10). DDS is characterized by the use of dopaminergic drugs in doses larger than those required to treat motor symptoms. The risk factors for addictions in PD include male sex, younger age or younger age of onset, history of substance use or bipolar disorder and personality profile characterized by impulsiveness (11). The ICD mechanism is not clearly explained. Dopamine agonists, occasionally MAO B inhibitors, in less frequency levodopa, can cause ICD (12). Garcia-Ruiz et al revealed that related to dopaminergic treatment the creativity of the patients was improved. Improved creativity is considered as a beneficial effect on the contrary to ICD. Since there is a relationship between ICD and improved creativity, it is inclined that medication-related improved creativity is associated with dopaminergic treatment. Pramipexole and ropinirole were found more related to creativity when compared to rotigotine (13). Hypersexuality is not only characterized by an increase of libido but also exhibitionism, excessive use of sex phone-in lines, prostitution services and sex shops (11). Administration of a dopamine agonist, especially if combined with L-Dopa, may induce these behavioural disorders, probably through the excessive stimulation of the D2 receptor and particularly of the D3 subclass (4).

Dopamine has an important role in the activity of medial preoptic anterior (MPOA) hypothalamic nuclei and stimulation of projections to the nucleus accumbens, both associated with sexual function so that dopaminergic therapy may affect sexual behaviour through the direct stimulation of the D2 receptor in the medial preoptic area Furthermore, by inhibiting prolactin secretion and increasing the plasmatic level of oxytocin, which produces erectogenic effects in the lumbosacral spinal cord, dopaminergic stimulation may lead to the resumption of sexual activity and hypersexuality in some patients.

The risk of aberrant sexual behaviour, such as hypersexuality and other forms of obsessive sexual deviation, is probably underestimated in PD patients being treated with high doses of L-Dopa or dopaminergic agonists (14). The pulsatile dopaminergic medication causes sensitization of the limbic ventral striatum and the motor dorsal striatum. This sensitization may lead to an alter from apathy to ICD. Jimenez-Urbieta et al proposed that levodopa-related dyskinesias and ICD could be included under the title of maladaptation to dopaminergic therapy (15). Fronto-striatal and cingulo-frontal dysfunction may show disability in metacognitive-executive capacities and causes compulsive recurrence of behaviour. In this regard, ICD could be somewhat described as a response-inhibition disorder (12). In PD patients, polymorphisms in dopaminergic genes have been found associated with ICD (12). Either greater discharge of dopamine or enhanced dopaminergic receptor stimulation can be the cause of ICD in Parkinson's patients (15).

In our patient, pramipexole caused hypersexuality unexpectedly. This case constitutes interesting findings in two ways; 1.5 mg/day pramipexole caused hypersexuality while no hypersexuality had occurred with the use of ropinirole after pramipexole withdrawal. Pramipexole is generally not the first-choice therapy for Parkinson patients older than 70 years. Because tremor was the most disabling and prominent feature, pramipexole was chosen for treatment. Our patient improved with pramipexole, however, the hypersexuality side effect had occurred. ICD has been thought to be associated with D3 stimulation (8). D2, D3, D4 dopaminergic receptors are stimulated by both pramipexole and ropinirole, but pramipexole's affinity on dopamine receptor D3 is higher than D2, D4 (16). That's why we switched treatment from pramipexole to ropinirole. Pathological hypersexuality may not be recorded for a variety of reasons: lack of awareness of the condition or shyness of patient, reluctance of patients or physicians. Recognition of abnormal sexual behaviour in PD is very important because it is harmful to the patient and their partners. Furthermore, it is a treatable condition (4).

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