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Pathological gambling and hypersexuality due to dopaminergic treatment in Parkinson's disease

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Introduction. Prevalence of psychiatric disorders in patients suffering from Parkinson's disease varies from 12 to 90%. The most common disorder in the natural evolution of Parkinson's disease is depression. However, episodes of psychosis and hypomania are related to treatment with L-dopa and dopaminergic agents. Other recognized, although less frequent, psychiatric disorders are hypersexuality and development of certain addictive behaviors, which is compulsive gambling and overdosing of anti-Parkinson agents.

Clinical case. A case is presented of a male patient diagnosed with Parkinson's disease at an early age who was treated with L-dopa and a combination of dopaminergic agents. During the course of his evolution he manifested symptoms of hypersexuality and pathological gambling which were unrelated to psychotic or mood changes.

Conclusions. A number of hospital admissions were needed into order to detect a pattern of abusive consumption of L-dopa as the main factor behind his behavior changes. The possibility of overdosage of L-dopa and dopaminergic drugs should be considered when there is pathological gambling conduct and/or hypersexuality, without psychotic or accompanying affective symptoms, in a male who develops Parkinson's disease at an early age and who undergoes treatment with these drugs and manifests motor fluctuations and dyskinesias.

Early detection of the presence of these alterations, included within those described as «dopaminergic dysregulation syndrome», would allow for an early intervention on the cause behind them and would hence avoid the possible medical and social complications.

Key words:
Parkinson's disease. Antiparkinson agents. Sexual dysfunctions. Pathological gambling.

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Juego patológico e hipersexualidad debidos a tratamiento dopaminérgico en la enfermedad de Parkinson

Introducción. La prevalencia de trastornos psiquiátricos en pacientes con enfermedad de Parkinson varía de un 12 a un 90%. La depresión es el trastorno más frecuente en la evolución natural de la enfermedad de Parkinson; mientras que las alteraciones psicóticas e hipomaniacas se relacionan con el tratamiento con L-dopa y agonistas dopaminérgicos. Otras patologías psiquiátricas reconocidas, aunque menos frecuentes, son la hipersexualidad y el desarrollo de determinadas conductas adictivas: juego patológico y sobredosificación de fármacos antiparkinsonianos.

Caso clínico. Se presenta el caso de un paciente varón diagnosticado de enfermedad de Parkinson a una edad temprana, tratado con L-dopa y distintos agonistas dopaminérgicos en combinación, que a lo largo de su evolución ha presentado hipersexualidad y conductas de juego patológico no relacionadas con alteraciones psicóticas ni del estado de ánimo.

Conclusiones. Fueron necesarios varios ingresos hospitalarios para reconocer una pauta de consumo abusivo de L-dopa como factor precipitante de las alteraciones conductuales. La presencia de conductas patológicas de juego y/o hipersexualidad, sin sintomatología psicótica ni afectiva concomitante, en un varón con enfermedad de Parkinson de inicio temprano, que realiza tratamiento con L-dopa y agonistas dopaminérgicos y presenta fluctuaciones motoras y discinesias debería alertar sobre la posibilidad de sobredosificación de estos fármacos.

Reconocer precozmente la presencia de estas alteraciones, englobadas en lo que se describe como «síndrome de desregulación dopaminérgica», permitiría una intervención temprana sobre la causa que lo provoca y evitaría las complicaciones tanto médicas como sociales que ocasiona.

Palabras clave:
Enfermedad de Parkinson. Antiparkinsonianos. Disfunción sexual. Juego patológico.

INTRODUCTION

Parkinson's disease (PD) is characterized by a loss of pigmented neurons of nigrostriatal system, giving rise to a depletion of dopamine neurotransmitter.

The main treatment is the correction of the dopamine defect through administration of levodopa (L-dopa) and/or dopaminergic agonists. Treatment with these drugs is associated to side effects such as digestive disorders, blood pressure alterations, depressive type psychic disorders, confusional state, excitation or psychoses and appearance of involuntary movements in the form of akathisia and dyskinesia. The latter generally occur due to use of high-doses and after a prolonged time

Dopaminergic agonists are combined with L-dopa, thus making it possible to decrease their dose and improve the dyskinesia and motor fluctuations related with its prolonged administration.

One adverse effect that can be attributed to the drugs that strengthen dopaminergic function is hypersexuality. This was observed initially with the use of apomorphine¹ or L-dopa² and after with dopaminergic agonists.^{3,4} This effect may be beneficial as it improves quality of life of the Parkinsonian patient with erection disorders or with low sexual impulse but harmful in others due to its manifested intensity and form, sometimes as disinhibition pictures that interfere with performing daily activities, causing deterioration in social relationships and sometimes having legal repercussions.⁵

More recently, pathological gambling behaviors have been related to treatment with dopaminergic drugs. This type of behavior could be related in some cases to compulsive consumption of these agonists^{6,7} that could be explained by an insufficiency of the dopaminergic reward system.⁸

Both hypersexuality and pathological gambling conducts are uncommon but when they do occur, they give rise to serious consequences for the patient and his/her family surroundings. It may be difficult to correctly diagnose it, its cause being attributed to a primary psychiatric disorder (psychosis or manic episode) and thus symptomatic treatment may be initiated that will be ineffective in the end as inadequate consumption of anti-Parkinsonian drugs with dopaminergic activity is continued.

CLINICAL CASE

The case of a 48-year old male at the time of the first psychiatric evaluation, diagnosed of PD since 11 years before, under treatment with L-dopa and different dopaminergic agonists, with compulsive gambling and hypersexuality, is presented.

At the onset of his disease, he received treatment with pergolide (up to 3 mg/day) and selegiline (up to 10 mg/day). It was necessary to modify the drug many times in the following years due to rapid clinical deterioration. After 6 years of evolution, motor fluctuations appeared with phenomena of end of dose and morning akinesia, so that L-dopa (300 mg/day) was added. Due to the persistence of mobility alterations and functional deterioration, the dose of L-dopa (400 mg/day) was increased and amantadine (300 mg/day) was added. Several months later, psychiatric symptoms such as anxiety, depressed mood, pathological gambling conducts in slot machines and occasionally brief psychotic episodes consisting in suspicions and delusional-type ideation of harm appeared, the already described movement alterations persisting.

All these circumstances, that is motor involvement characteristic of PD, pathological gambling episodes and psychotic pictures, finally generated a situation of family and financial instability and social vulnerability, separation from spouse, going into debt and poverty.

In his first psychiatric admission, he received anti-Parkinsonian treatment with: Carbidopa/L-dopa (250/1000mg/day), entacapone (1000 mg/day), ropinirol (20 mg/day), selegiline (10 mg/day) and amantadine (200 mg/day). The reason for admission was fear of being attacked, a fear related with a sexual exhibition episode that had occurred one month earlier, after pergolide was replaced by ropinirol. At the beginning of the hospitalization, he had a suspicious attitude and verbalized delusional-type contents of harm in reference to aggression and robberies previously suffered. He admitted obsessive gambling behaviors and abuse consumption of L-dopa, doubling the dose prescribed, which he had hidden up to then. All the alterations described rapidly improved when the anti-Parkinsonian drug was adjusted, although it was necessary to add quetiapine (300mg/day) as symptomatic treatment. The prescription of discharge recommended by the Neurology Department was: Carbidopa/L-dopa (250/1000 mg/day), entacapone (1000 mg/day), ropinirol (20 mg/day), and selegiline and amantadine were withdrawn.

A few days after discharge from his first admission, he abandoned antipsychotic treatment and reinitiated L-DOPA abuse. One month later, the patient was readmitted due to behavioral disorganization and heteroaggressivity. During this admission, a clearer sexual disinhibition, verbal provocations towards other hospitalized patients, exhibitionistic behaviors and compulsive masturbation became manifest. These alterations were not accompanied by expansive mood and abated when the anti-Parkinsonian treatment was readjusted. The complementary test may need (cranial computed axial ultrasonography and electroencephalogram) had no significant pathological findings.

A final contact in the emergency department of the hospital occurred five months after discharge from his second admission due to an episode of exhibitionism. He was in

custody of the police as a detainee. Psychiatric and neurological evaluation was requested. This psychopathological examination showed no psychotic symptoms or symptoms having a maniform nature. The patient admitted that he had been doubling the L-dopa daily dose based on the alterations in mobility and his motivational condition.

DISCUSSION

At present, the treatment base of PD is pharmacological with L-dopa and dopaminergic agonists (table1).

The benefits of replacement therapy in the psychiatric setting include a sensation of well-being, recovery of interest regarding the surroundings and improvement of depressive feelings, of apathy and cognitive function, especially in auditory perception and verbal understanding. Recovery of interest in sexuality accompanying improvement of motor capacities has also been acknowledged for some time.⁹

The adverse psychiatric effects appear according to different authors at a rate ranging from 10% to 50% of the patients treated.⁹ Psychotic symptoms are the most fre-

quent.¹⁰ They may even become more incapacitating than the motor disorders themselves. The psychotic disorders induced by anti-Parkinsonism treatment can be classified in accordance with the presence or non-presence of awareness level disorders: delusions with a significant dream component or delusional ideas and visual hallucinations or olfactory hallucinations, respectively. Restlessness and agitation, hypomania, hypersexuality, impulsivity, depression, anxiety and insomnia have also been observed. These complications seem to appear at any time of the treatment, but are most frequent in the advanced stages.

In relationship to the sexual alterations in the context of Parkinson's Disease, Klos et al³, point out the combination of L-dopa with dopaminergic agonists as the principal cause. All the articles reviewed reflect the greater incidence of hypersexuality and other alterations in the sexual sphere in men.^{3,11}

Regarding pathological gambling conducts, different observational studies have indicated that the principal causal agents are treatment with pramipexol and ropinirol.¹² According to other publications, the risk that the mentioned psychiatric disorder could appear would be similar with different anti-Parkinsonian agents: L-dopa, pramipexol, per-

| Table 1 | Drugs used in Parkinson's disease |
|---------|---|
| | Precursor of dopamine: Levodopa/carbidopa (Levodopa: it crosses blood-brain barrier. It is metabolized in dopamine on the central level; in combination with carbidopa: inhibitor of peripheral dopa decarboxylase) |
| | Dopaminergic Agonists: (they act on the post-synaptic dopaminergic D2 receptors) |
| | <i>Non-ergot derivatives:</i> Pramipexol Ropinirol |
| | <i>Ergot derivatives:</i> Pergolide (also D1 and D2 agonist properties) Cabergoline Bromocriptine Lisuride (it also has serotonergic activity) |
| | <i>Derivative of morphine:</i> Apomorphine (D1 and D2 agonist) |
| | MOA-B Inhibitors: (selective inhibition of monoamino oxidase B) Selegiline |
| | COMT Inhibitors: (O-methylation inhibitors of dopamine) Entacapone Tolcapone |
| | Antivirals: (for influenza a virus, with dopaminergic activity) Amantadine |
| | Antimuscarinics: (anticholinergics) Biperidene Trihexifenidil |

golide or ropirinol.^{8,13} In the Molina et al. study⁹ it is indicated that pathological gambling conducts appear almost exclusively with the *on* period and could be related with an increase of dopaminergic tone secondary to drug treatment of PD:

There is great individual variability in the predisposition to suffer these complications:¹² genetic burden, character traits, premorbid mental state or background of psychiatric disorder could be risk factors.

The case presented could belong to a group of patients with PD whose cognitive and conductual alterations can be attributed directly to the increase of the drug dose beyond that needed to treat the patient's motor alterations. All these alterations would be included in the Dopaminergic Dysregulation Syndrome (DDR).⁶ The patients who fulfill this pattern of abusive consumption of L-dopa and/or dopaminergic agonists have in common that they are more frequently men with relatively early onset of the PD. In many occasions, complex strategies are put into practice to accumulate medication and not accept the attempts to readjust the treatment. The presence of dyskinesias induced by abuse of these drugs does not stop its consumption. With the progressive increase of the doses, hypomanic episodes, psychomotor agitation, irritability, intolerance to frustration or euphoria can be precipitated. Thought alterations and delusional-type ideation of harm may appear. These symptoms tend to abate with the decrease or interruption of the treatment.⁷ More specific clinical aspects of DDS, characterized by impulsivity and tendency to compulsion, would be catalogued as: *a)* «craving» that can appear even in absence of withdrawal and provoke taking the next dose early, as if it was a dependency; *b)* appetite disorders with bingeing episodes; *c)* hypersexuality, manifested as frankly ill-adapted behaviors: exhibitionism, excessive use of pornography or prostitutes (extreme cases of zoophilia¹⁴ or travestism¹⁵ having been described); *d)* pathological gambling; *e)* compulsive shopping and *f)* compulsive ordering behaviors, of assembly and disassembly, of classifying objects, all with no specific purpose («punding»).

Giovannoni et al.⁷ established diagnostic criteria to recognize this syndrome that they called «hedonistic homeostatic dysregulation» characterized by:

1. Pathological consumption: overdosing to relieve motor alterations; poisoning that can be accompanied by severe dyskinesias and mental state alterations.
2. Deterioration in social functioning beyond that which can be attributed to the incapacitating symptoms of PD: divorce, social rejection, economic problems due to excessive costs, legal problems due to inappropriate sexual behaviors or aggressivity.
3. Tolerability: recognizable due to the unpredictably short duration of the therapeutic effects of a dose, that also is

accompanied by dyskinesias and by the need to increase the amount to experience pleasure. Sometimes, the patient is only capable of perceiving an activated state when serious dyskinesias develop. Once they disappear, he/she feels in an «off state» in spite of persistence of psychomotor fluidity.

4. Withdrawal: under mood state characterized by anxiety, dysphoria, irritability or depression. This leads the patients to seek medication and accumulate it due to the anxiety of being short of supplies.

The way of acting when faced with these complications would begin at the time when anti-Parkinsonian treatment is begun, informing the patient of the possibility of their appearance, especially in those patients with risk factors to present them. Once treatment is initiated, precise anamnesis that makes it possible to rule out or recognize their existence as soon as possible should be made.¹³ Finally, when they are present, decrease the anti-Parkinsonian dose and initiate symptomatic treatment with antipsychotics: olanzapine,^{3,7} quetiapine,^{6,7,11} risperidone or clozapine.^{6,7}

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