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Chronic Dopamimetic Drug Addiction and Pathologic Gambling in Patients with Parkinson's Disease - Presentation of Four Cases

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Abstract

Parkinson's disease (PD) is characterized by motor and neuropsychiatric features. Within the latter, conditions such as psychosis, obsessive compulsive disorder (OCD), levodopa addiction and pathologic gambling are considered as secondary to the use of dopamimetic drugs. We present four patients with PD who developed clinical criteria for levodopa and pathologic gambling addiction, generalized anxiety disorder and OCD. They were 3 males and 1 female, with an average age of 65.8 years. They had been under levodopa treatment for a mean of 8.5 years. They used levodopa on an arbitrary basis, with an average dose of 2250 mg/d and bromocriptine with an average dose of 38.75 mg/d. None of them had a history of major depression, anxiety or OCD.

The mechanism involved in anxiety seen in PD is deemed to be an imbalance between dopamine and norepinephrine, whereas OCD has been correlated with basal ganglia and dopaminergic mesolimbic subsystem dysfunction. The dopaminergic system and basically the mesolimbic subsystem and accumbens nucleus are deemed to be directly involved because both mediate reinforcement and rewarding processes that have a crucial role in drug-addiction mechanisms. This dopaminergic hypothesis is embedded in the biological theory of gambling addiction.

We believe that these patients illustrate how PD progresses and dopaminergic treatment may cause these neurobehavioral disorders, beside the important role played by basal ganglia and the dopaminergic system on behavior (German J Psychiatry 2002;5:62-66).

Keywords: Parkinson's disease, pathologic gambling, dopaminergic reward system, addiction, levodopa, obsessive-compulsive disorder

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Introduction

Parkinson's disease (PD) is characterized by motor and neuropsychiatric disorders (Friedman et al, 2000). Within the latter, conditions such as dementia (Mindham et al, 2000), depression (Poewe et al, 1999), anxiety (Walsh et al, 2001) and disexecutive disorder (Foti et al, 1997) are recognized as belonging to this disease.

Other symptoms such as psychosis (Wolters, 1999), obsessive compulsive disorder (OCD) (Alegret et al, 2001), levodopa addiction and pathologic gambling (Giovannoni et al, 2000) are considered as secondary to the use of dopamimetic drugs.

The mechanism involved in anxiety seen in PD is deemed to be an imbalance between dopamine and norepinephrine. In normal individuals, mesencephalic dopamine reduces the locus coeruleus release range, which is the main noradrenergic nucleus; and anxiety is attributed to an exaggerated noradrenergic activity (Walsh et al, 2001;

gerated noradrenergic activity (Walsh et al, 2001; Marsh, 2000), whereas OCD has been correlated with basal ganglia and dopaminergic mesolimbic subsystem dysfunction (Alegret et al, 2001: Micallef et al, 2001).

With regard to addiction and pathologic gambling, the dopaminergic system and basically the mesolimbic subsystem and accumbens nucleus (Cummings, 2000) are deemed to be directly involved because both mediate reinforcement and rewarding processes that have a crucial role in drug-addiction mechanisms (Spanagel et al, 1999). This dopaminergic hypothesis is embedded in the biological theory of gambling addiction (Moreyra et al, 2000).

We present four patients with PD who developed clinical criteria for levodopa and pathologic gambling addiction, generalized anxiety disorder and OCD.

Patients

This is a series of clinical cases from a third level reference health care unit specialized in movement disorders, who were assessed by the author. None of the patients came for consultation voluntarily; they were all brought by relatives.

They were 4 patients, 3 males and 1 female, with an average age of 65.8 years. Clinical and demographic characteristics are listed in Table 1. The disease had an average duration of 9.5 years under levodopa treatment for a mean of 8.5 years. They used levodopa on an arbitrary basis, with an average dose of 2250 mg/d and bromocriptine with an average dose of 38.75 mg/d. None of them had a history of major depression, anxiety disorders or OCD.

Their average scores at ON status (a patient who has the best response from medication, indicating that the striatal dopamine receptors are capable of responding to the medication) on both Hoehn and Yahr scales (H&Y) and Unified Parkinson's Disease Rating Scale: motor section (UPDRms) (Fahn et al, 1987) were 2.12 and 68.5, respectively. They achieved a 70% depressive score on the Hamilton Depression Scale (Hamilton, 1960), 51.25 scores on the Beck Anxiety Inventory (Beck et al, 1988), and 24.5 scores on the Mini-Mental State (MMS) (Folstein et al, 1975). All patients presented fluctuations in their levodopa response and significant dyskinesia (Quinn's N classification) (Quinn, 1998) for dose peak or square wave (3 patients) and diphasic dyskinesia (1 patient). All of them met ICD-10 (World Health Organization, 1992) criteria for generalized anxiety disorder, pathologic gambling, substance abuse, and OCD.

All patients were under the following treatment: (i) progressive reduction (3-6 month range) of dopamimetic drugs down to levels prescribed before their disorder; (ii) use of fluoxetine with a dose varying between 60 and 120 mg/d; and, (iii) psychotherapy. Follow-up carried out later (8-26 month range) was proven to lead to substantial improvement in 2 patients and complaint resolution in the remaining patients.

Patient 1

A 69-year-old male patient with PD for 8 years, under levodopa treatment for 7 years. The patient came with his

Table 1. Clinical and Demographic Characteristics of the Patients

Patient No.	Age (years)	Gender	PD (years)	Levodopa treatment (years)	H & Y	UPDRS (motor score)	Hamilton Depression Scale (%)	Beck Anxiety Inventory (score)	MMS	Levodopa dose prescribed/ actually taken mg/d	Bromocriptine dose prescribed/ actually taken mg/d	Other medicines mg/d
1	69	M	8	7	2.5	78	65	51	25	1375/2000	22.5/37.5	propranolol 120, amitriptyline 25
2	71	M	11	11	2	61	70	48	24	1250/2250	17.5/45	amitriptyline 25, selegiline 10
3	64	F	9	7	2	58	65	55	23	1500/2250	15/30	fluoxetine 40
4	59	M	10	9	2	77	80	51	26	1625/2500	25/42.5	amitriptyline 50, propranolol 160
Mean (± SD)	65.8 (5.37)		9.5 (1.11)	8.5 (1.65)	2.13 (0.25)	68.5 (10.47)	70 (7.07)	51.25 (2.87)	24.5 (1.29)	1437.5 (161.37)/ 2250 (204.12)	20 (4.56)/ 38.75 (6.61)	

PD (years) = duration of Parkinson´s disease in years; H&Y = Hoehn and Yhar, UPDRS motor score= motor section of the UPDRS; levodopa treatment (years) = duration of levodopa treatment in years; MMS = Mini Mental State (Folstein et al., 1975); M = male; F = female; SD = standard deviation; Hamilton Depression Scale = 76 to 100% (50 to 67 points, severe depression); 51 to 75% (32 to 49 points, severe depression; 26 to 50% (14 to 31 points, moderate depression); and, 0 to 25% (0 to 13 points, mild depression)

wife because, for the past 13 months, he had been taking levodopa doses increasingly higher than those prescribed, even though it was obvious that this drug overuse was accompanied by severe diphasic dyskinesia. At the time dyskinesia reached its peak, the patient became euphoric, whereas if dyskinesia resolved, the patient said he felt tired, "restless", irritable, discouraged and disheartened, with shaking, palpitations, tachypnea, nausea, fear and urge to flee. The patient spent considerable amounts of money on lottery tickets and antiparkinson medication. He had even misappropriated some items from his home to sell them and procure the money he required. When his wife and children confronted him, he told them he "could not stop doing so" and suffered terrible anguish if he did not take an extra dose of levodopa and buy lottery tickets, despite admitting "I have never won anything". On the other hand, the patient used to spend a lot of time repeatedly checking that his home lights were off and asking any person he saw to turn off the lights. He was aware that this attitude was ridiculous, and feared being considered a "nut", but it was beyond his control and will. If he overcame it occasionally, he was plagued by the irrational fear of a light bulb exploding and the house burning down.

Patient 2

A 71-year-old male patient with PD of 11-year evolution and levodopa treatment thereafter. He came on the insistence of his sister who was worried because 15 months ago the patient had started spending his money to buy antiparkinson drugs (levodopa and bromocriptine) and lottery tickets beyond control. The patient had dose-peak euphoria and concurrent dyskinesia that in spite of its severity did not keep him from going out to buy lottery tickets. Whenever he had no money or could not buy either drugs or lottery tickets, he felt pessimism and anguish, and every attempt to avoid this drive was followed by profuse sweating, flushing, chest pressure and severe fear of suffering a cardiac infarction. He begged for money to buy what he wanted, understanding that his behavior was irresponsible, but saying that an inner force compelled him to do so.

Alternatively, the patient had an intense preoccupation with the presence of ants in his apartment. He spent several hours daily hunting them by spraying insecticides or placing poison on every corner; he said that if he did not kill them, they would swallow him up. It was not uncommon for him to wake up at midnight and go hunting ants or suddenly start doing so while he had visitors. If someone tried to stop him by reasoning with him about his absurd behavior, he felt embarrassed, but after a few minutes started to present diaphoresis, agitation, generalized itching, and he scratched vigorously all over his body.

Patient 3

A 64-year-old woman who was diagnosed to have PD 10 years ago and was under levodopa treatment for 9 years. She came at her son's insistence because, since approximately 15 months previously, she had been taking anti-Parkinson medication (levodopa and bromocriptine) at doses higher than those prescribed. She presented a varying response to treatment and peak dose-induced dyskinesia. She got into debt with several people to buy lottery tickets and drugs. When her family discovered this, she acknowledged that it was happening, but was not aware of how it had started. This was a feeling she was not able to control and despite the fact that she knew it was wrong, she could not remedy it. Any attempt to avoid buying tickets was associated with a strong feeling of anxiety and failure to remain quiet, flushing, nausea, headache, and diarrhea, accompanied by a fear of her parkinsonian symptoms worsening. Likewise, when she did not take drugs, she became "nervous", felt pain over her entire body and a severe precordial oppression. On the other hand, she had developed a repetitive behavior consisting of brushing herself, spending many hours trying to do so, which was hindered by her motor disorder. She frequently asked her daughters, nephews or daughters-in-law to brush her and when they stopped, she kept on doing so herself. If she could not find a hairbrush, she would call up one of her children and ask them to bring one for her urgently because if she did not brush her hair, she had a headache. When she was asked about her tendency to comb herself, she answered that she felt as if her hair was slithering on her head, a movement that caused her pain and created the need for brushing her hair. When she was not able to do so, she felt unbearable pain. She was ashamed of feeling this. She had visited a few dermatologists who had never found any injury on her scalp.

Patient 4

A 50-year-old male patient with PD over 10 years and on levodopa treatment for 9 years. He came with his wife because, 18 months previously, he had started getting into debt with various relatives in order to buy antiparkinson drugs and lottery tickets, and over the last month he had bought over 150 tickets from a single lottery seller. He suffered severe dyskinesia and a concurrent feeling of self-assurance and urgent sexual drives. When this period ended, he withdrew and was fearful of being seen by other people. When he could not go out to buy what he desired, he developed generalized tremor, abdominal itching, nausea, flushing, dyspnea, and severe anguish for not been able to get out of “that hole”.

A year ago, he started changing his clothing and taking a shower several times a day (about 7 times) and eating quite frequently (about 10 times). When his wife objected to his

behavior, he said that he smelled bad. When the patient was confronted with this problem, he felt upset, recognizing it was an exaggerated behavior and adding that he was afraid of smelling bad and being rejected by his family and friends.

Discussion

These patients pose two diagnostic considerations. One of them is developing a dopamimetic drug addiction syndrome; the other is the pathologic gambling which, in our opinion, is intermingled with the addictive problem and OCD, the latter being involved in the whole notion of anxiety disorders.

In PD, the major dopaminergic system affectation involves the participation of motor structures (cortex, striatum, pallium and nucleus accumbens) and non-motor structures (cortex, striatum, pallium, nucleus accumbens, tonsil and the limbic cortex complex) (Nakano et al, 2000; Nakano, 2000; Braak et al, 2000; Swanson et al, 1998), which accounts for the motor and neuropsychiatric symptom complex.

The following have been found in patients with PD: (i) a close correlation between gambling addiction and ON status (corresponding to peak plasmatic levodopa levels) (Molina et al, 2000); (ii) levodopa and pathologic gambling addiction (Gschwandtner et al, 2001); (iii) development of OCD following basal ganglia injuries (Chacko et al, 2000); (iv) occurrence of OCD in patients in later stages of this pathology (Alegret et al, 2001); and, (v) prevalence of anxiety reaching 40% in these patients (Walsh et al, 2001; Marsh, 2000). The unifying element for all these facts is the dopamine deficiency that characterizes PD (Braak et al, 2000; Damier et al, 1999).

It is known that the V10 tegmental area of the dopaminergic neurons is the generator of rewarding and learning behaviors mediating addiction (Spanagel et al, 1999) and that these neurons themselves also take part in the sequential procedural learning (motivation of the rewarding-based procedural learning), (Hikosaka et al, 1999). The involvement of this neuronal group is, in our belief, essential for the development of addiction and pathologic gambling in our patients, in addition to the OCD. For instance, the obsessive compulsion of brushing her hair in patient 3 may be considered as a type of displacement activity (self-directed behavior) related to certain non-flight behavior which have been shown to attenuate stress physiological indicators and whose ultimate origin is the prefrontal cortical dopaminergic response to stress (Micallef et al, 2001).

All our patients met the ICD-10 criteria for generalized anxiety disorder, addiction and OCD. While there are various hypotheses to explain pathologic gambling, it is clear that dopamine is involved in its physiopathology and that it may be considered as a part of the OCD or a non-pharmacological addiction (Moreyra et al, 2000), both disorders playing a role in pathologic gambling. To support the supposition that pathologic gambling is involved in the OCD in our patients, we point out that a syndrome named lottery compulsive disorder (Calder, 2001) has been described recently. We cannot claim that lottery compulsive disorder is definitely involved in our patients, since access to other forms of gambling may have been very difficult for them, compared with the abundant, easy, practical and affordable purchase of lottery tickets.

A greater compulsion to gamble was concomitant with ON stages in these patients. Refusal to gamble and failure to take dopamimetic drugs generated anxiety. All of them were aware of this problem. They also maintained appropriate introspection regarding the useless nature of their obsessive-compulsive rituals. We believe that these patients illustrate how PD progresses and dopaminergic treatment may cause these neurobehavioral disorders, beside the important role played by basal ganglia and the dopaminergic system on behavior.

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