Low frequency of bipolar disorder, dopamine dysregulation syndrome, and punding in Brazilian patients with Parkinson's disease

Baixa frequência de transtorno bipolar, síndrome de desregulação dopaminérgica e punding em pacientes brasileiros com doença de Parkinson

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Abstract

Objective: To investigate the frequency of bipolar disorder, dopamine dysregulation syndrome and *punding* in Parkinson's disease patients from a Brazilian movement disorders clinic. **Method:** One hundred patients underwent a comprehensive psychiatric examination composed of MINI-plus and specific questionnaires to investigate dopamine dysregulation syndrome and *punding*. **Results:** We identified, respectively, one and five Parkinson's disease patients with bipolar disorder type I and type II. All manic/hypomanic episodes occurred before Parkinson's disease onset. No patient was identified with dopamine dysregulation syndrome or *punding*. **Conclusion:** The frequency of manic/hypomanic episodes seems to decrease with Parkinson's disease onset, and local environmental factors (e.g. drug availability) may be responsible for the low frequency of dopamine dysregulation syndrome and *punding* in Brazilian Parkinson's disease patients.

Descriptors: Parkinson disease; Bipolar disorder; Syndrome; Patients; Brazil

Resumo

Objetivo*: Investigar a frequência de transtorno bipolar, síndrome de desregulação dopaminérgica e* punding *em pacientes com doença de Parkinson de uma clínica de movimentos anormais no Brasil.* ***Método:*** *Cem pacientes foram submetidos à avaliação psiquiátrica composta pelo MINI-Plus e questionários específicos para investigar síndrome de desregulação dopaminérgica e* punding*.* ***Resultados:*** *Identificamos, respectivamente, um e cinco pacientes com transtorno bipolar tipo I e tipo II. Todos os episódios maníacos/hipomaníacos ocorreram antes do início da doença de Parkinson. Nenhum paciente foi identificado com síndrome de desregulação dopaminérgica ou* punding*.* ***Conclusão:*** *A frequência de episódios maníacos/hipomaníacos parece declinar com o início da doença de Parkinson. Fatores ambientais locais (p.ex.: disponibilidade de drogas) podem ser responsáveis pela baixa frequência de síndrome de desregulação dopaminérgica e* punding *em pacientes brasileiros com doença de Parkinson.*

Descritores: *Doença de Parkinson; Transtorno bipolar; Síndrome; Pacientes; Brasil*

Introduction

The "monoaminergic theory" is considered an important biological basis for the comprehension of neuropsychiatric disorders.[1] Parkinson's disease (PD), a degenerative condition resulting in predominantly dopamine depletion at *pars compacta* from substantia nigra, may provide relevant insights into this matter. Dysfunction of the dopaminergic neurotransmission may underlie the pathophysiology of some psychiatric disorders which have their frequency increased in PD.

Recently dopamine has been suggested to be involved in the neurobiology of bipolar disorder.[2] A subgroup of PD patients undergoing therapy with high-dose dopaminergic agents can present the so-called Dopamine Dysregulation Syndrome (DDS). The core features of DDS are self-medication, levodopa-seeking and hoarding associated with disabling mood and behavioral changes.[3] In DDS, mood dysregulation comprises alternation between depressed and elated affect, and is frequently associated with hypersexuality, aggression,

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pathological gambling, compulsive shopping and social isolation, resembling a bipolar-like syndrome.[2-4] An additional behavioral disorder supposedly associated with changes in dopaminergic neurotransmission is *punding*, which consists of repetitive, stereotyped, aimless and disrupted behaviors related to the person's past work or hobby.[5,6]

In a previous study by our group we found that the lifetime frequency of bipolar I and II disorders in PD seems to be similar to that observed in the general population.[7] By contrast, the prevalence of unipolar depression in PD was significantly increased.[7] In the present study we investigated the frequency of bipolar disorder, DDS, and *punding* in a sample of Brazilian PD patients.

Patients and methods

1. Subjects

One hundred (M/F: 56/44) outpatients with idiopathic PD were consecutively recruited from the Movement Disorders Clinic of the Universidade Federal de Minas Gerais (UFMG), Brazil. Patients with previous neurosurgery, other neurologic disorder, *delirium* or dementia were excluded. Dementia was diagnosed according to DSM-IV diagnostic criteria and to the score obtained in the Mini-Mental State Examination (MMSE) adapted for the Brazilian population.[8]

2. Clinical assessment

Demographic and clinical data were obtained. Neurological examination included the MMSE, the Unified Parkinson's Disease Rating Scale (UPDRS), the Hoehn-Yahr Scale (HY), and the Schwab-England Scale of Activities of Daily Living (SES). Patients were examined in the "on" state. The UPDRS was used to assess PD severity and it included all of its subsections (I to IV). The HY was used to estimate disease stages, while disability in performing activities of daily living was assessed with the SES.

Patients underwent a standardized psychiatric examination, which included the Mini-International Neuropsychiatric Inventory (MINI-Plus), and structured questions related to the diagnosis of DDS and *punding*.

The MINI-Plus is an internationally validated short-structured diagnostic psychiatric interview,[9] compatible with the DSM-IV and ICD-10 criteria. DDS was investigated with the short screening questionnaire designed by Pezzella et al.,[4] which was based on the diagnostic criteria for DDS published in the seminal paper by Giovannoni et al.[10] In brief, the questions comprised the overuse of dopaminergic agonists or levodopa, associated with mood or behavioral changes. These questions were directed to both patients and their caregivers as suggested by the authors.[4] We also asked questions related to behaviors suggestive of *punding* as proposed by Evans et al.[5]

The patients provided informed consent and the study was approved by the Ethics Committee of the UFMG (protocol CAAE-0048.0.203.000-06).

3. Statistical analysis

Descriptive statistics are presented with the corresponding 95% confidence interval.

Results

A hundred PD patients participated in this study. No patient refused to participate. Patients had a mean age (standard deviation) of 56.8 (10.5) years and mean age of PD onset of 47.3 (11.4) years (Table 1). The mean disease duration was 9.5 (5.9) years. Seventy (70%) patients were taking levodopa (Table 2), with a mean (SD) dose of 608.5 (302.5) mg/day. Four additional patients (4%) had already used levodopa, but they had the drug withdrawn due to disabling dyskinesias. Another 46% were taking other dopaminergic agents (35% taking pramipexole and 11% taking bromocriptine). The mean daily levodopa equivalent unit dose[5] was 560.4 (365.4).

Manic and hypomanic episodes were found in, respectively, one and five PD patients. A 95% confidence interval for manic episode was 0% to 2.95%, while this confidence interval for hypomania was 0.73% to 9.27%. These episodes were confirmed by patients' caregivers or relatives. All manic or hypomanic episodes occurred before disease onset and no further episodes were identified after PD development. However, among the six patients with manic/hypomanic episodes we found three that presented depressive episodes after PD onset, and in two of them depression was controlled with sertraline without switching to mania. All PD patients with a history of bipolar disorder had motor fluctuations

Table 1 - Continuous variables sampling statistics

Variables	Mean (SD)	95% Confidence Interval	
		Lower limit	Upper limit
Age, years	56.8 (10.5)	54.74	77.38
Age of onset, years	47.3 (11.4)	45.07	69.6
Disease duration, years	9.5 (5.9)	8.34	21.1
UPDRS, score	50.1 (25.9)	45.02	100.9
Schwab-England Scale, score	80.9 (13.6)	78.23	107.6
Levodopa, mg/day	608.5 (302.5)	549.21	1201.4
Levodopa equivalent unit	560.4 (365.4)	488.78	1276.6
MMSE, score	26.4 (3.5)	25.71	33.26

SD, standard deviation; UPDRS, Unified Parkinson Disease Rating Scale; MMSE, Mini-Mental State Examination.

Table 2 - Categorical variables sampling frequencies

Variables		Frequency	95% Confidence Interval	
			Lower limit	Upper limit
Gender	Male	56	46.27%	65.73%
	Female	44	34.27%	53.73%
Hoehn-Yahr	Stage 1	12	5.63%	18.37%
	Stage 2	40	30.40%	49.60%
	Stage 3	41	31.36%	50.64%
	Stage 4	7	2.00%	12.00%
Levodopa	Not on	30	21.02%	38.98%
	On	70	61.02%	78.98%
On levodopa				
With dyskinesias		42	48.52%	71.48%
Without dyskinesias		28	28.52%	51.48%

but with no related significant mood swings. Further clinical data of these patients are presented in Table 3.

No case of DDS or *punding* was diagnosed in the studied patients.

Discussion

In the current study, we observed a frequency of bipolar I disorder of 1% and of bipolar II disorder of 5% in patients with PD. The frequency of bipolar disorders in the general population has been estimated to range from 1 to 5% by different studies,[11,12] which is within the confidence intervals of our data. Moreover, we did not find any patient with DDS or *punding*.

Our results raise some intriguing issues. First, PD patients with a history of bipolar disorder did not present any further manic or hypomanic episodes after PD onset, although all of them were taking levodopa and two of them were taking an antidepressant. Thus, the prevalence of life-time bipolar disorder (i.e. manic/hypomanic episodes) seems to be close to what is expected in the general population before PD onset, but the frequency of manic/hypomanic episodes may decrease thereafter.

Second, not a single patient with DDS was identified in this cohort. This may suggest that the frequency of this syndrome may be lower in Brazilian patients. Of note, the frequency of DDS is estimated to be 4% in tertiary centers like ours.[4,10] Phenomenology of DDS may be influenced by cultural and environmental factors as is its frequency.[4] This lower frequency in our patients may be related to some of these environmental factors. Some drugs with a fast onset of action, including apomorphine, which may act as a catalyst for DDS,[13] are not available in Brazil. Furthermore, our patients usually have difficulties affording dopaminergic agents or levodopa. Hence, they acquire medication in public pharmacies with a restrictive drug dispensation, preventing drug hoarding. It has been well established that drug availability is an important risk factor for drug abuse[14] and this was not taken into account in previous studies investigating DDS. Although other risk factors, such as young-onset male patients and higher dopaminergic drug intake, are relevant for the clinician in preventing DDS,[4] drug availability should be considered by health policy makers.

Dopamine may be involved in pathophysiology of bipolar disorder, as the frequency of manic/hypomanic episodes after PD onset seems to decrease. However, care should be taken in considering that a single monoamine is responsible for the heterogeneous phenotypes of neuropsychiatric disorders. For example, although dopamine plays a relevant role in schizophrenia, the frequency of psychosis in PD is not decreased and it is not necessarily related to dopamine replacement therapy.[15] Also, bupropion, an antidepressant which increases synaptic dopamine and noradrenaline levels, is less prone to induce manic switches than sertraline and venlafaxine, antidepressants with smaller effect on dopaminergic neurotransmission.[16] In PD, decreased dopaminergic levels may affect the frequency of manic and

Table 3 - Clinical characteristics of patients with Parkinson's disease and bipolar disorder

No.	Gender	Age	Age of onset	Hoehn-Yahr	UPDRS	Medications
1*	F	60	47	2	47	Levodopa (500mg), amantadine, lorazepam, valproate
2	M	39	29	2	25	Levodopa (500mg), pramipexole, amantadine
3	M	72	67	2	32	Levodopa (500mg), buspirone
4	F	73	60	2	22	Levodopa (500mg), sertraline
5	M	62	54	3	81	Levodopa (1250mg), sertraline, diazepam
6	F	59	43	4	115	Levodopa (625mg), pramipexole, amantadine, antihypertensive drugs

** Patient with bipolar I disorder*
UPDRS, Unified Parkinson's Disease Rating Scale

depressive episodes. Nevertheless, dopamine replacement therapy is not always able to treat non-motor symptoms of PD, and these patients respond to antidepressants with serotonergic mechanism of action. Thus, the relationships among neurotransmitters are far more complex than we can imagine.

Our study has some clear limitations. For instance, the patient diagnosed with bipolar I disorder was still taking a mood stabilizer. Furthermore, our screening for DDS was based on self-report of medicine usage which is not the "gold standard" in adherence monitoring.[17] Our sample might also be considered too small to detect DDS and punding, especially taking into account that not many patients were in high-dose therapy of dopaminergic drugs. Nevertheless, a significant proportion of the patients enrolled in this study (50%) had early-onset PD, a well-known risk factor for these behavioral disorders,[4] which may be considered as strength of this study. The prevalence of punding was initially estimated to be 14% within patients with high-dose therapy.[5] Recently, this frequency was estimated at 1.4% in non-selected patients.[6] We believe this later estimate is more accurate as we could not detect any patient with *punding*.

In conclusion, the frequency of manic/hypomanic episodes seems to decrease with PD onset. The small sample size and the low mean of daily levodopa equivalent unit dose may be responsible for the low frequency of DDS and *punding* in Brazilian PD patients but local environmental factors such as drug availability must also be considered in future studies as a potential determinant of the prevalence of DDS.

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Disclosures

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Arthur Kummer	UFMG	-	-	-	-	-	-
Fernando M. V. Dias	UFMG	-	-	-	-	-	-
Francisco Cardoso	UFMG	FAPEMIG*	-	-	-	-	-
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** Modest*
*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*
Note: UFMG = Universidade Federal de Minas Gerais; FAPEMIG = Fundação de Amparo à Pesquisa do Estado de Minas Gerais; CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico.
For more information, see Instructions for authors.

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