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Gac Med Mex. 2016;152:321-6

GACETA MÉDICA DE MÉXICO **ORIGINAL ARTICLE**

Prevalence of neuropsychiatric disorders in drug-naive subjects with Parkinson's disease (PD)

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Abstract

Introduction: *Parkinson's disease is characterized by a broad spectrum of neuropsychiatric manifestations. Its pathophysiology has been associated with the disease itself as well as with the dopaminergic treatment.* **Material and Methods:** *A cross-sectional study was conducted in drug-naive patients with early Parkinson's disease. All participants were evaluated through a set of scales for specific neuropsychiatric symptoms including: cognition, depression, anxiety, apathy, psychosis, and impulse control disorder.* **Results:** *A total of 63 patients with Parkinson were included, of whom 26 (41.3%) subjects had some degree of cognitive impairment; seven (11.1%) had depression and 11 (15.8%) subjects had anxiety. Regarding the other symptoms, a total of 12 (19%) patients showed apathy, seven (11.1%) had psychosis, and eight (12.6%) patients had symptoms related to impulse control disorders.* **Conclusion:** *Neuropsychiatric disorders are common in drug-naive patients with early Parkinson's disease. Given the impact of these symptoms on quality of life, identification and proper treatment is essential.* (Gac Med Mex. 2016;152:321-6)

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KEY WORDS: *Parkinson's disease. Cognitive decline. Depression. Anxiety. Apathy. Psychosis. Impulse control.*

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease. PD is estimated to affect 1 to 2% of the population older than 60 years of age[1]. Although PD is generally recognized as a condition with motor involvement, already since his original descriptions Charcot made reference to the neuropsychiatric manifestations of PD. Moreover, the premorbid personality of subjects with PD has been previously described as emotional, attitudinal and inflexible, with introversion and depressive tendency[2].

Neuropsychiatric disorders have important repercussions on patients, as well as on their caregivers. Hence, it is desirable for these symptoms to be recognized as soon as possible, given their potential impact on disease progression and even on patient survival[3].

Most frequently described neuropsychiatric alterations in subjects with PD include cognitive deterioration, dementia, impulse control disorder, apathy, depression and anxiety, psychosis and hallucinations. The reported frequency of any type of psychiatric symptoms is higher than 60%[4].

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This investigation required no funding.
There are no conflicts of interests on behalf of any of the authors.

Date of modified version reception: 28-07-2015
Date of acceptance: 01-08-2015

With regard to these neuropsychiatric manifestations' pathophysiogenesis, different alterations have been described in different catecholaminergic systems (dopamine, noradrenaline, serotonin) of PD itself[4]. As a counterpart, dopaminergic replacement therapy itself can trigger or increase these symptoms through stimulation of different dopamine receptors[5].

Based on the above, it is of majo interest knowing the neuropsychiatric profile of PD-diagnosed subjects prior to receiving the indicated antiparkinsonian treatment. This information will facilitate intentional search for the most prevalent disorders, will provide adequate follow-up and will prevent, or at least decrease, the risk for medication-derived adverse effects.

The purpose of the present study is to determine the prevalence of neuropsychiatric disorders in treatment naïve subjects with newly diagnosed PD.

Material and method

A cross-sectional study was carried out at the National Institute of Neurology and Neurosurgery *(Instituto Nacional de Neurología y Neurocirugía).* PD-diagnosed patients of the Movement Disorders Clinic attended to within the period encompassed between March 1, 2012, and December 31, 2014. The PD diagnosis was based on compliance with the United Kingdom Parkinson's Disease Society Brain Bank Criteria for PD[6]; in all cases, the assessment was performed by a neurologist specialized in movement disorders. PD patients with serious systemic comorbidities or with seriously compromised health status within the 3 months prior to the evaluation and that at clinical consideration of the assessors might impact on the mental capacities of the subject, were excluded. Additionally, subjects with clear audition (serious hypoacusis) or vision disturbances (amblyopia or blindness) or inadequate general health status to perform the assessments and interviews were also excluded.

After a medical appointment, the subjects were invited to participate in the study. All patients granted written informed consent according with the requirements of the Bioethics Committee. The subjects with PD were assessed with the clinical instruments described below.

Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS). MDS-UPDRS is a multidimensional, structured scale for the assessment of PD symptoms and their functional consequences that currently is considered a consensus tool and is widely used. This scale is comprised by 4 domains: I: Non-motor experiences of daily living (0-52 points); II: Motor experiences of daily living (0-52 points); III: Motor examination (0-108 points), and IV: Treatment-derived complications (0-24 points)[7].

Hoehn and Yahr severity stages (HY). The HY scale allows for PD subjects to be classified according to disease severity. This scale is comprised by 5 stages; stages 1 and 2 correspond to mild disease, stage 3 to moderate disease and stages 4 and 5 to severe disease[8].

PD quality of life questionnaire (PDQ-8). This PD-specific scale assesses 8 aspects of health-related quality of life. Evaluated domains are mobility, activities of daily living, emotional well-being, social stigma, support network, cognition, communication and bodily discomfort. Each item is qualified in a Likert scale, and total score is transformed into a simplified index (ranging from 0 to 100) that indicates the extent patients' quality of life is globally affected (values close to zero indicate better quality of life)[9]. Additionally, a visual analogue scale was applied for health-related global quality of life; in this instrument, the subject had to select one point of the scale from 0% (worst possible status) to 100% (best possible status).

Montreal Cognitive Assessment (MoCA). This instrument examines the following cognitive skills: attention, concentration, executive functions (including abstraction ability), memory, language, visuoconstructive abilities, calculation and orientation. Maximum possible score is 30. Based on the score, subjects are categorized into normal cognition (26 to 30 points), mild cognitive deterioration (18 to 25 points), moderate cognitive deterioration (10 to 17 points) and severe cognitive deterioration (0 to 9 points)[10].

Brief Psychiatric Rating Scale (BPRS). This scale is used to rapidly assess for the presence of psychotic symptoms and other related symptoms. The BPRS has a total of 126 points. Based on the scores, the following groups are obtained: "borderline" state (25 to 30 points), mildly affected (31 to 40 points), moderately affected (41 to 53 points) and considerably affected (54 or more points)[11].

Dys-executive Questionnaire (DEX-Sp). DEX-Sp is an instrument comprised by 20 items. The questionnaire evaluates the following areas: problems with abstract thought, impulsivity, fabrication, difficulties for planning, euphoria, trouble with temporal sequencing, lack of insight, apathy, lack of inhibition, difficulty to control impulses, superficial affective responses, aggression, lack of interest or perseverance, restlessness, inability to inhibit responses, dissociation between knowledge and answers, distractibility, poor judgment in decision making and disregard for social rules. Each item is scored on a 5-point Likert scale, ranging from "never"

Table 1. Summary scores in the clinimetric instruments applied to the study population

	Mean	Standard deviation	Minimum	Maximum
Total MDS-UPDRS	40.5	22.6	14	148
MDS-UPDRS I	4.6	5.9	0	25
MDS-UPDRS II	8.9	6.8	0	41
MDS-UPDRS III	27	12.9	10	85
HY	2.4	0.8	1	4
PDQ-8	40.6	12.7	10	75
Global quality of life	55.3	20.9	0	100
MoCA	25.3	3.6	21	30
DEX-Sp	14.5	11	0	32
BPRS	25.5	5.4	18	46
HADS anxiety	5.7	4.4	0	18
HADS depression	5.6	4.1	0	18
LARS	–19.3	9.7	–34	7
QUIP-RS	6.7	9.3	0	39

MDS-UPDRS: Movement Disorders Society Unified Parkinson's Disease Rating Scale; HY: Hoehn & Yahr scale; PDQ-8: PD quality of life questionnaire; MoCA: Montreal Cognitive Assessment; DEX-Sp: Dys-executive questionnaire; BPRS: Brief Psychiatric Rating Scale; HADS: Hospital Anxiety and Depression Scale; LARS: Lille Apathy Rating Scale; QUIP-RS: Questionnaire for Impulsive Disorders in Parkinson's Disease.

(0 points) to "very often" (4 points), for a total of 80 points. Based on the score, the following cutoff points are obtained: no symptoms (< 14 points); normal (14 to 23 points); mild-to-moderate dysfunction (24 to 32 points), moderate-to-serious dysfunction (33-41 points) and very serious dysfunction (> 41 points)[12].

Hospital Anxiety and Depression Scale (HADS). This scale comprises two 7-question series: one represents the anxiety subscale, and the other the depression subscale, with both psychopathologic concepts being independent. Each item is scored according to a 4-point frequency scale ranging from 0 to 3. Scores above 10 are considered to be consistent with morbidity. An 8-10 score is interpreted as a borderline case, and scores lower than 8 indicate absence of significant morbidity[13].

Lille Apathy Rating Scale (LARS). The LARS scale is a useful tool for the diagnosis of apathy in PD. It is an instrument administered by the interviewer and refers to the patient's situation within the 4 weeks prior to the interview. It comprises a total of 33 items and the score ranges from -36 to +36 (the higher the score, the higher the apathy). To diagnose apathy using LARS, the presence of cognitive deterioration and depression has to be ruled out. Ranges of involvement are categorized as follows: normal (–36 to –22 points), mild (–21 to –17 points), moderate (–16 to –10 points) and severe (–9 to +36 points)[14].

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP-RS). The QUIP-RS is comprised by 4 main questions (relative to frequent thoughts, desires and impulse control disorder-associated behaviors), each one applied to the main symptoms of impulse control disorder (pathologic gambling, compulsive shopping and compulsive sexual behavior), as well as to associated disorders (excessive use of medications, compulsive acts and hobbyism). A 5-point Likert scale (0-4 score for each question) is used to measure the frequency of behaviors, and the patients are instructed to answer the questions based on behaviors that have been produced within the previous 4 weeks (or any 4-week period within a designated time-frame). Total score for all impulse control disorders and disorders related to the combination ranges from 0 to 112. Each domain has a cutoff point to demonstrate involvement, with the gambling domain being ≥ 6, shopping ≥ 8, ≥ sex ≥ 8, eating ≥ 7, the sum of all 4 domains ≥ 10, hobbies and simple activities ≥ 7. For the purposes of the present study, only the presence of any of the aforementioned symptoms was

considered in order to obtain a dichotomous classification[15].

Statistical analysis. Qualitative variables are presented in terms of percentage, and quantitative variables in means and standard deviations. The relationship of the PDQ-8 score with the neuropsychiatric scales scores was explored by means of Pearson's correlation coefficient.

Results

A total of 63 patients were assessed, out of which 61.9% (n = 39) were males and 38.1% (n = 24) females. Mean age was 57.8 ± 10 years. Mean level of education was 9.8 ± 4.6 years. Mean evolution time since the onset of motor symptoms at diagnosis was 21.7 ± 15.8 months.

As for clinical presentation, 68.2% (n = 43) of patients had a predominant tremor-dominant phenotype, 23.8% (n = 15) an akinetic-rigid syndrome and only 7.9% was classified as having postural and gait instability predominance. The side of symptoms onset was the right in 57.1% (n = 36) of cases.

The summary of scores for all different clinimetric instruments are shown in table 1. Total MDS-UPDRS mean score was 40.52 ± 22.6 points. In the case of motor evaluation of the scale (MDS-UPDRS part III), the mean was 27 ± 12.9 points. Disease severity according to the HY scale was as follows: mild in 88.9% (n = 56) of cases, moderate in 7.9% (n = 5) and severe in 3.2% (n = 2) of the subjects with PD.

With regard to quality of life, the PDQ-8 simplified index mean was 40.6%. However, in the visual analogue scale assessing health related global quality of life, the mean was 55.3 ± 20.9%, which in general terms equates to a mediocre to poor quality of life.

In the cognitive aspect, presence of cognitive deterioration was detected in 41.3% (n = 26) of the subjects by applying the MoCA scale. In most cases, cognitive deterioration was of the mild type (80% of cases).

The presence of dys-executive symptoms was detected in 19% (n = 12) of the subjects by means of the DEX-Sp scale. Among these subjects, 41.7% (n = 5) had mild-to-moderate dysfunction; 33.3% (n = 4), moderate-to-serious dysfunction, and 25% (n = 3), very serious dysfunction.

As for psychosis and related disorders, a total of 25 subjects (39.7%) were in "borderline" state, whereas 4 subjects (6.3%) were mildly affected and 3 (4.8%) were classified as being moderately affected. No subjects were considerably affected. Overall, the frequency of psychosis was 11.1%.

The scores for the HADS scale, including the anxiety and depression subscales are shown in table 1. The prevalence of any degree of depression was 11.1% (n = 7), although 12 subjects more (19%) were classified as borderline. In the anxiety subscale, 15.8% (n = 11) of the subjects were categorized as having anxiety with clinical involvement; additionally, 8 subjects (12.7%) were considered as borderline.

With regard to apathy, its diagnosis by means of the LARS scale required for cognitive deterioration and depression to be absent. For this, the MoCA scale was used according to the cutoff value of 26 points to define the absence o presence of cognitive deterioration and the HADS scale (depression subscale), using a cutoff value of 7 or less points to define the absence of depressive symptoms. The prevalence of apathy in the sample was 19% (n = 12).

Finally, presence of at least one impulse control disorder or related symptoms was identified in 12.6% (n = 8) of the study population.

When the PDQ-8 simplified index score was correlated with each one of the scores of the applied instruments, it was moderately correlated with BPRS (r: 0.48; p = 0.01), the HADS anxiety subscale (r: 0.46; p < 0.01) and the HADS depression subscale (r: 0.49; p < 0.01). The correlation was very low with total MDS-UPDRS (r: 0.04; p = 0.03) and DEX-Sp (r: 0.20; p < 0.01). There was no significant correlation with MoCA, LARS or QUIP-RS.

Discussion

PD can be accompanied by a broad spectrum of neuropsychiatric symptoms, some of them resulting from the treatment of the disease, while others are the consequence of pathophysiologic disturbances of the disease itself. In the present study, the prevalence of the main neuropsychiatric symptoms is described in subjects with PD without exposure to any kind of dopaminergic replacement therapy. A battery of clinical instruments was used for the detection of neuropsychiatric symptoms. It should be noted that all clinimetric instruments have been used and validated in populations with PD.

The main neuropsychiatric conditions in PD include cognitive deterioration. Several etiologies have been proposed with regard to cognitive alterations, mainly involving disruption of the cholinergic system, as well as failures in dopaminergic and other neurotransmitters' transmission in the striatum. A reduction in 18F-dopa uptake in the ventral striate nucleus and the cingulum has been documented in subjects with Parkinsonism and dementia[16]. On the other hand, a decrease in

noradrenergic, serotonergic and cholinergic impulse due to a decline of neuronal population of the locus coeruleus, the raphe nuclei and nucleus basalis of Meynert, respectively, has been also reported[17]. Finally, there is global cortical atrophy in the entorhinal region, as well as a blood flow decrease in several association cortical areas[18].

The prevalence of mild cognitive deterioration in the present study was 33.3%. This figure is higher than the 26.7% reported in international literature[19,20]. This discrepancy may be the consequence of the effect of other confounders, such as the level of education, which is relatively low in our center. On the other hand, MoCA is a screening test with higher sensitivity and specificity in comparison with other instruments such as the Mini-mental State Examination, particularly in subjects with PD. This is because the MoCA evaluates a higher number of domains and emphasizes on typically affected areas in PD, such as visuospatial tasks[21]. Moreover, it should be pointed out that MoCA is a screening rather than definitive diagnosis instrument. Nevertheless, even considering these points, the prevalence of cognitive deterioration was higher than expected and specific studies are required in our population including a complete neuropsychological evaluation.

Dysexecutive symptoms are part of the cognitive functions. Executive functions are referred to the processes by means of which the subject optimizes his/her performance in complex tasks comprising many components. The dysexecutive syndrome is characterized by the following disturbances: inability to initiate, stop and modify a behavior in response to a changing stimulus; inability to carry out a series of consecutive actions that allow for a problem to be solved; and inability to organize a plan of action and inability to inhibit inappropriate responses and perseveration or abnormal repetition of a behavior. The frequency of these symptoms in our study population was 19% by means of the use of DEX-Sp[22].

Psychotic symptoms in PD develop from a complex interaction of intrinsic and extrinsic factors. Attributing the phenomenon exclusively to the action of drugs is currently not accepted. Pathophysiological and anatomical investigations have focused on 3 primarily affected areas: the primary visual system, the brainstem function and cortical dysregulation[23].

The BPRS scale was used in the present study. The BPRS has no properly defined cutoff point; however, based on its correlation with the disease global impression scale, it is possible to categorize the subjects according to the score obtained[11]. In our study, an 11.1% frequency was found using the BPRS. The prevalence of psychosis in PD has been reported to range from 20 to 40% depending on the instrument employed[24]. The low frequency found in our population is explained by the absence of risk factors such as the use of dopaminergic agonists, old age and prolonged duration of the disease.

The prevalence of depression and anxiety, with 11.1 and 15.8%, respectively, is consistent with the lower limits reported in the literature, with an approximate prevalence of 15 to 30% in patients with PD[25]. It should be considered that these prevalences vary according to the employed instrument. Biochemically, depression and anxiety share similarities in patients with PD; they are due not only to dopaminergic depletion in the mesolimbic system, but also to a decrease in the noradrenergic and serotonergic flow on structures such as the insula, the anterior cingulus, the thalamus, the locus coeruleus, the amigdala and the ventral striate[26].

The prevalence of apathy in treatment naïve patients is not known and the studies in treated patients show an important variability in terms of results being dependent on factors such as cognitive deterioration, affective symptoms and the scales used in the analysis. The LARS scale was used in our study, with a prevalence of 20% being found in the absence of depression or cognitive deterioration. Prevalence in a study similar to the present one in untreated patients with PD was 19%[26]. As for pathophysiology, a significant association has been reported of apathy with cognitive deficit, but not with motor deficit, suggesting that non-dopaminergic circuits could be related to the development of apathy[27].

Finally, the prevalence of impulse control disorders was 13%, comparable to the 6% to 14% reported in previous studies[28]. Impulse control disturbance appears to be associated with a dopaminergic dysregulation on D3-type receptors at the level of the corticomesolimbic system[29].

With regard to quality of life, the disorders most related to decreased quality of life were depression, anxiety and psychosis, whereas apathy, cognitive deterioration and impulse control disorder appear not to relate to it.

Our study has limitations to be considered. The study has the limitations inherent to a cross-sectional design, and, for this reason, a cohort has been formed with the participating subjects in order to make a follow-up and compare the effects of dopaminergic therapy on the frequency of neuropsychiatric disorders. Furthermore, the absence of healthy control subjects in the present study precludes establishing if there are differences in

the frequency of neuropsychiatric disorders between subjects with PD and healthy subjects. This issue was not the purpose of the study; in addition, the higher prevalence of these problems with regard to the general population has already previously been described[30]. The finding of frequencies in untreated subjects with PD that are comparable to those reported in treated patients allows for higher prevalence than in healthy subjects to be inferred. Recently, Weintraub et al. described that the frequency of depression, anxiety, apathy, impulse control disorder and psychosis as measured by means of MDS-UPDRS part I is twice as high in subjects newly diagnosed with PD in comparison with healthy controls[20]. With regard to the relatively limited sample size of our study, it should be highlighted that Weintraub's multicenter study included an average of 26 patients per participating center. Another limitation is that the scales used are mainly screening instruments and, therefore, the results cannot be considered as a definitive diagnosis of the presence of a type of neuropsychiatric disorder. The study was conducted in a tertiary care referral hospital and, consequently, enrollment of treatment naive patients was lower in comparison with a first-contact center.

In conclusion, neuropsychiatric symptoms are quite frequent in patients with early PD not exposed to any dopaminergic replacement therapy. This suggests that these symptoms are an integral part of the disease since its beginning and might be related to disease progression. The importance of neuropsychiatric disturbances in PD is being increasingly recognized owing to their repercussions on the patients' functionality and overall quality of life; therefore, knowing their prevalence warrants inclusion of their intentional search in daily clinical practice in order to offer adequate neuropsychiatric care and have a better clinical profile of each patient, which will enable a more personalized selection of pharmacological treatment for the disease.

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