Factors associated with cognitive impairment in a Mexican multicenter Parkinson's disease cohort: a cross-sectional comparative study

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Abstract

Introduction: Cognitive impairment is common in Parkinson's disease and represents a risk for dementia. Identifying associated factors will help implement early interventions and study its progression. **Objective:** To identify factors associated with cognitive impairment. **Method:** Cross-sectional study of 306 subjects with Parkinson's disease who were assessed for 12 months. Demographics and clinical variables were analyzed as explanatory variables, and cognitive impairment as outcome variable. Significant variables were used to construct a cognitive impairment predictive model. **Results:** Cognitive impairment was reported in 43.8%. Female gender ($p = 0.001$, odds ratio [OR] = 1.77), age at diagnosis ($p < 0.001$, mean deviation [MD] = 5.7, level of education ($p < 0.001$, MD = -2.9), disease duration ($p = 0.003$, MD = 1.7) MDS-UPDRS part III score ($p < 0.001$, MD = 9.7), presence of anxiety ($p = 0.007$, OR = 2.11), hallucinations ($p = 0.029$, OR = 2.27) and freezing of gait ($p = 0.048$, OR = 1.91) were predictors for cognitive impairment. The use of type B monoamine oxidase inhibitors was associated with less cognitive impairment ($p = 0.001$). **Conclusions:** Predictive factors that were consistent with those previously reported were identified. Prospective studies are required in order to clarify the effect of type B monoamine oxidase inhibitors on cognition.

KEY WORDS: Cognitive impairment. Non-motor symptoms. Parkinson's disease. Monoamine oxidase inhibitors.

Factores asociados con deterioro cognitivo en una cohorte mexicana multicéntrica de Parkinson: estudio transversal comparativo

Resumen

Introducción: El deterioro cognitivo en Parkinson es común y representa un riesgo para demencia. Identificar los factores asociados ayudará a implementar intervenciones tempranas y estudiar la progresión del deterioro cognitivo. **Objetivo:** Identificar factores asociados con deterioro cognitivo. **Método:** Estudio transversal de 306 sujetos con Parkinson evaluados durante los últimos 12 meses. Se estudiaron variables demográficas y clínicas como explicativas y el deterioro cognitivo como desenlace. Las variables significativas se utilizaron para construir un modelo predictor de deterioro cognitivo. **Resultados:** El 43.8 % reportó deterioro cognitivo. El sexo femenino ($p = 0.001$, RM = 1.77), edad al diagnóstico ($p < 0.001$, desviación media [DM] 5.7), escolaridad ($p < 0.001$, DM -2.9), duración de enfermedad ($p = 0.003$, DM 1.7), puntuación en MDS-UPDRS

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parte III ($p < 0.001$, DM 9.7), presencia de ansiedad ($p = 0.007$, RM = 2.11), de alucinaciones ($p = 0.029$, RM = 2.27) y congelamientos de la marcha ($p = 0.048$, RM = 1.91) fueron predictores para deterioro cognitivo. El uso de inhibidores monoamina-oxidasa tipo B se asoció con menor deterioro cognitivo ($p = 0.001$). **Conclusiones:** Se identificaron factores predictores consistentes con lo reportado previamente. Se requieren estudios prospectivos para aclarar el efecto de los inhibidores monoamina-oxidasa tipo B en la cognición.

PALABRAS CLAVE: Deterioro cognitivo. Síntomas no motores. Parkinson. Inhibidores de monoaminooxidasa.

Introduction

Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by classic motor symptoms such as bradykinesia, resting tremor, rigidity¹ and a wide variety of non-motor symptoms that may occur during the course of the disease, including cognitive dysfunction.² In PD, cognitive dysfunction can vary from mild cognitive impairment (MCI) to dementia. MCI in PD has been reported in 18.9 to 57.1 % of patients.^{3,4} In previous studies of Mexican PD cohorts, a prevalence of cognitive impairment of 39 to 41.3 % was reported.^{5,6} The MCI profile in PD is mainly characterized by executive dysfunction, attention and visuospatial skills alterations, in addition to episodic memory problems and difficulty to find words.⁷ In addition, MCI predicts the development of dementia, which can occur in up to 80 % of the population with PD during the course of the disease,⁸ where the development of dementia is significant and has a substantial impact on independence, admission to nursing homes, psychiatric comorbidities, burden for the caregiver, and mortality risk.^{9,10}

Recent studies have reported demographic and clinical risk factors for cognitive impairment in PD such as age at onset, depression, anxiety, level of education, baseline measurements of disease severity, gender, olfactory dysfunction and hallucinations.¹¹⁻¹⁴ In addition to clinical characteristics, associated factors have also been found: mutations (B-glucocerebrosidase gene),¹⁵ thinning of the cerebral cortex,¹⁶ cerebral white matter lesions¹⁷ and cerebral amyloid load.¹⁸ For this reason, we consider early recognition of cognitive impairment in PD to be of vital importance in order for strategies to reduce these outcomes to be implemented. With the purpose to identify factors associated with cognitive impairment in our population, we analyzed demographic and clinical variables, which will help to increase the knowledge about cognitive impairment risk factors and the possibility to detect subjects at risk for developing dementia in the course of the disease and, in addition, it will provide bases for future prospective study designs.

Method

Cross-sectional, descriptive, analytical, observational clinical study, to examine and identify factors associated with symptoms of cognitive impairment in a sample of Mexican subjects with PD. The study subjects were selected from the Mexican Parkinson Study Group cohort, constituted by 306 subjects with PD assessed during 2017 and 2018 and consecutively included. A neurologist specialist in movement disorders established the PD diagnosis according to criteria of the Movement Disorder Society (MDS).¹⁹ The subjects come from five Parkinson and movement disorders clinics of the country: Technological Institute of Monterrey, Christus Muguerza High Specialty and Christus Muguerza Southern Hospital of Monterrey, General Hospital of Mexico, Regional Hospital of the Institute of Social Security and Services of State Workers and National Institute of Neurology and Neurosurgery, Mexico. All subjects of the Mexican Parkinson Study Group cohort were included for analysis. The present study was approved by the institutional ethics committee.

For explanatory variables, demographic and clinical characteristics of the subjects were documented. Demographic characteristics included gender, current age, age at diagnosis and years of education. Clinical characteristics included disease duration, side of symptom onset (right, left, bilateral), PD motor subtype: tremor-dominant, postural instability with gait difficulty, intermediate, Hoehn and Yahr stage, drugs used (levodopa, dopaminergic agonists and types thereof [pramipexole or rotigotine, catechol-O-methyltransferase inhibitors, monoamine oxidase type B inhibitors [MAOBI and types thereof [rasagiline or selegiline, amantadine, levodopa equivalent daily dose) and MDS-modified unified Parkinson's disease rating scale (MDS-UPDRS) parts I, II, III, IV and total scores. MDS-UPDRS is the validated scale to assess patients with PD and consists of four parts:²⁰

- Part I (non-motor experiences of daily living), which consists of 13 items.

Table 1. Comparison of demographic and clinical characteristics of our cohort in subjects with *versus* without the presence of cognitive impairment symptoms (n = 306)

Variable	Cognitive impairment (n = 134)		No cognitive impairment (n = 172)		p
	Mean ± SD		Mean ± SD		
Age at diagnosis (years)	63.5 ± 11.5		57.8 ± 12.2		< 0.001
Current age (years)	69.2 ± 10.9		62.2 ± 11.4		< 0.001
Level of education (years)	8.9 ± 5.1		11.8 ± 5.1		< 0.001
Disease duration (years)	7.6 ± 5.3		5.9 ± 4.2		0.003
LEDD (mg)	744.0 ± 455.9		739.5 ± 499.2		0.935
MDS-UPDRS I score	10.5 ± 6.8		6.3 ± 4.9		< 0.001
MDS-UPDRS II score	6.3 ± 7.0		4.5 ± 4.3		0.010
MDS-UPDRS III score	41.3 ± 16.9		31.7 ± 13.2		< 0.001
MDS-UPDRS IV score	3.3 ± 4.4		2.3 ± 3.7		0.054
MDS-UPDRS total score	61.5 ± 24.3		44.8 (18.6)		< 0.001
	n	%	n	%	
Females	74	55.2	61	35.5	0.001
Right side symptom onset	63	47.0	96	55.8	0.122
PD PIGD subtype	78	58.2	82	47.7	0.185
Hoehn and Yahr stage I-III	116	86.6	165	95.5	0.003
Levodopa	115	85.5	141	82.2	0.367
Dopaminergic agonist	67	50.0	92	53.5	0.545
MAOB inhibitor	9	6.7	34	19.8	0.001
COMT inhibitor	1	0.7	8	4.7	0.083
Amantadine	26	19.4	26	15.1	0.322

PIGD = Postural instability and gait difficulty, PD = Parkinson's disease, DA = dopaminergic agonist. MAOBI = monoamine oxidase type B inhibitors, COMT = catechol-O-methyltransferase, LEDD = levodopa equivalent daily dose, MDS-UPDRS = Movement Disorder Society-Unified Parkinson Disease Rating Scale.

- Part II (motor experiences of daily living), which consists of 13 items.
- Part III (motor examination), which consists of 18 items.
- Part IV (motor complications), which consists of 6 items.

Each item of the scale is scored from 0 to 4, where 0 is considered normal and 4, severe. At the end, the scores are added up to determine each part's total score and the scale total score. The higher the score, the worse the clinical status. In addition to demographic variables, as clinical explanatory variables, the presence of non-motor symptoms was documented using all MDS-UPDRS part I 13 items, presence of gait difficulties (MDS-UPDRS items 2.12 and 3.10) and presence of freezing of gait (items 2.13 and 3.11). To

identify the presence of symptoms of cognitive impairment (categorical outcome variable), MDS-UPDRS item 1.1 was used. For purposes of the study and practice at the clinic, the presence of any symptom was recorded if the item score was 1 to 4 and absence thereof if the score was 0.

Descriptive statistical analysis was carried out with measures of central tendency and dispersion. Means with standard deviations were analyzed for continuous variables, and frequencies with percentages were used for categorical variables. For the comparison of categorical variables, the chi-square test was used, and for variables with non-normal distribution, logarithmic transformation, as appropriate (symptom-onset side, catechol-O-methyltransferase inhibitors, type of MAOBI). Assumptions of variables' distribution were

verified with Kilmogorov-Smirnoff test. For the comparison of continuous variables means, Student's t-test was applied for variables with normal distribution (current age, age at diagnosis, level of education, MDS-UPDRS parts III, IV and total score) and log-transformation was used for variables with non-normal distribution, as appropriate (disease duration, years since diagnosis, levodopa equivalent daily dose, MDS-UPDRS parts I and II score).

In the multivariate analysis, a multiple logistic regression model was constructed to classify the patients with or without the presence of cognitive impairment symptoms. Variables with statistical significance ($p \leq 0.05$) were included and the model with less deviation was obtained, which was constructed with 80 % of the data and validated with the remaining data. For the goodness-of-fit assessment, the Hosmer-Lemeshow test was used. The calculations were carried out with the statistical program SPSS (Statistical Package for the Social Sciences), version 25.

Results

Of our total cohort of 306 subjects, 134 (43.8 %) were identified with symptoms of cognitive impairment. Table 1 describes the demographic and clinical characteristics of the study cohort, comparing subjects with and without cognitive impairment symptoms. The univariate analysis indicated that the female gender ($\chi^2_{1df} = 11.9$, $p = 0.001$), older age at diagnosis ($t [304] = 4.2$, $p < 0.001$), less years of education ($t [304] = 4.8$, $p < 0.001$), longer disease duration ($t [246.6] = 2.9$, $p = 0.003$), Hoehn and Yahr stage IV-V ($\chi^2_{1df} = 8.8$, $p = 0.003$), no presence of MAOBI ($\chi^2_{1df} = 10.6$, $p = 0.001$) and higher total scores in MDS-UPDRS part I ($t [232.2] = 6.1$, $p < 0.001$), part II ($t [209.6] = 2.6$, $p = 0.010$), part III ($t [246.5] = 5.4$, $p < 0.001$) and part IV ($t [304] = 6.8$, $p < 0.001$) were significantly associated with cognitive impairment symptoms.

Table 2 compares the presence of other non-motor symptoms based on MDS-UPDRS part I with the presence of cognitive impairment symptoms. The univariate analysis reported that the presence of symptoms of hallucinations and psychosis ($\chi^2_{1df} = 15.0$, $p < 0.001$), depression ($\chi^2_{1df} = 7.2$, $p = 0.007$), anxiety ($\chi^2_{1df} = 12.7$, $p < 0.001$), apathy ($\chi^2_{1df} = 8.9$, $p = 0.003$), sleep disorders ($\chi^2_{1df} = 4.6$, $p = 0.031$), urinary problems ($\chi^2_{1df} = 6.8$, $p = 0.009$), constipation ($\chi^2_{1df} = 7.0$, $p = 0.008$), postural hypotension symptoms ($\chi^2_{1df} = 5.5$, $p = 0.019$) and excessive salivation ($\chi^2_{1df} = 9.8$, $p = 0.002$) were significantly associated with cognitive impairment

Table 2. Comparison of the presence of non-motor symptoms and gait impairment between subjects with vs. without cognitive impairment symptoms (n = 306)

Variable	Cognitive impairment (n = 134)		No cognitive impairment (n = 172)		p
Hallucinations and psychosis	37	27.6	18	10.5	< 0.001
Depression	89	66.4	88	51.2	0.007
Anxiety	69	51.5	54	31.4	< 0.001
Apathy	33	24.6	20	11.6	0.003
Dopaminergic dysregulation syndrome	10	7.5	7	4.1	0.199
Sleep disorders	82	61.2	84	48.8	0.031
Daytime sleepiness	67	50.0	83	48.3	0.782
Pain	69	51.5	82	47.7	0.507
Urinary problems	87	64.9	86	50.0	0.009
Constipation	82	61.2	79	45.9	0.008
Postural hypotension symptoms	43	32.1	35	20.3	0.019
Fatigue	86	64.2	92	53.5	0.060
Excessive salivation	33	24.6	19	11.0	0.002
Gait disturbances	126	94.0	144	83.7	0.005
Freezing of gait	39	29.1	47	27.3	0.731

symptoms. The analysis also revealed that gait disturbances (MDS-UPDRS items 2.12 and 3.10) were significantly associated with cognitive impairment symptoms ($\chi^2_{1df} = 7.7$, $p = 0.005$).

Table 3 shows the significant variables used to construct the multiple logistic regression model to predict the presence of cognitive impairment symptoms. Gender, age at diagnosis, disease duration, level of education, MDS-UPDRS part III score, symptoms of hallucinations and psychosis, anxiety and freezing of gait were significant predictors of cognitive impairment symptoms. The final model showed a $r^2 = 0.254$, $p = 0.030$, with an accuracy of 72.5 % (95 % CI = 67.0-77.5).

Discussion

In a multi-center Mexican Parkinson cohort, the cognitive impairment predictive model demonstrated that the female gender, older age at diagnosis, less years of education, longer duration of disease, higher

Table 3. Multiple logistic regression model identifying predictors of the presence of cognitive impairment symptoms.

Variable	Coefficient (β)	Standard error	Wald (χ^2)	p	Exp (β)	95% CI
Constant	-5.14	1.11	—	—	—	—
Level of education	-0.08	0.03	8.03	0.005	0.93	0.88-0.98
Age at diagnosis	0.04	0.01	10.68	0.001	1.04	1.02-1.07
MDS-UPDRS part III	0.04	0.01	14.53	< 0.001	1.04	1.02- 1.06
Disease duration	0.10	0.03	8.82	0.003	1.10	1.03-1.17
Female gender	0.57	0.28	4.34	0.037	1.77	1.03-3.01
Freezing of gait	0.65	0.33	3.93	0.048	1.91	1.01- 3.64
Anxiety	0.75	0.28	7.19	0.007	2.11	1.22-3.64
Hallucinations/psychosis	0.82	0.37	4.79	0.029	2.27	1.09-4.72

MDS-UPDRS=Movement Disorder Society-Unified Parkinson's Disease Rating Scale. Our model predicts the presence of cognitive impairment symptoms with a certainty of 72.5% (95% CI = 67.0-77.5), sensitivity of 70.8% (95% CI = 63.8-77.1), specificity of 73.7% (95% CI = 69.1-77.7), positive predictive value of 63.4% (95% CI = 57.2-69.0) and negative predictive value of 79.7% (95% CI = 74.8-84.0).

MDS-UPDRS part III score and the presence of hallucinations and psychosis, anxiety and freezing of gait are significant predictors for cognitive impairment symptoms.

The results are similar to those of other previously analyzed cohorts. The prevalence of cognitive impairment symptoms in our cohort (43.8 %) is consistent with those reported in previous Mexican studies (39 to 41.3%)^{5,6} and falls within the international range (18.9 to 57.1 %).^{3,4} Among the predictive factors of our model, age, level of education, baseline measurements of clinical severity, disease duration, hallucinations, anxiety and freezing of gait have been reported as risk factors in international cohorts.¹² The discrepancy with other investigations with regard to gender might be explained by the lower level of education in our group of female subjects in comparison with male subjects (9.51 versus 11.37, $p = 0.002$).

The univariate analysis indicated a significant association between the use of MAOBI and a lower frequency of cognitive impairment (6.7 % versus 19.8 %, $p = 0.001$). However, said variable had no weight enough to be included in the final regression model. It is suggested that MAOBIs provide a benefit in cognition for its enhancing effect on dopaminergic central transmission. When the MAOBI types were separately analyzed, the use of selegiline was associated with lower presence of cognitive impairment, although not significantly (22.2 % versus 35.3 %, $p = 0.693$). Studies with rasagiline and selegiline have been limited and contradictory. Most studies with rasagiline have indicated a non-significant effect on cognition in

PD,²¹⁻²⁴ and most studies with selegiline, although positive, are few and of limited epidemiological design.²⁵⁻²⁷ Selegiline probable positive effect on cognition might be explained by its action on monoaminergic systems.²⁸ We consider that prospective studies on cognition in PD are needed to confirm the effect of MAOBIs, specifically of selegiline.

The present study has several limitations. The sample calculation was by convenience, and it is therefore subject to bias and may have influenced the final model. Since the type of study entails limitations, to reduce associated bias and control for possible confounding variables, we constructed an analytical regression model. We tried to reduce the selection bias by including a multicenter cohort. The measure used to classify the presence of non-motor symptoms, specifically cognitive impairment, is not the most adequate for this purpose. We did not consider other reported risk factors for cognitive impairment in Parkinson such as genetic factors, thinning of the cerebral cortex, amyloid accumulation or cerebral white matter lesions. However, the results raise the possibility of carrying out prospective studies to assess the factors associated with cognition in PD that we identified.

Conclusions

Our results identified risk factors for the presence of cognitive impairment symptoms that are consistent with those reported in previous studies. Apparently, the female gender was more affected in our cohort

owing to its lower level of education. Prospective studies are required to clarify the effect of MAOBIs on the cognition of patients with PD.

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