ORIGINAL ARTICLE

The impact of depression on survival of Parkinson's disease patients: a five-year study

O impacto da depressão na sobrevida de pacientes com doença de Parkinson: cinco anos de estudo

Cláudia Débora Silberman[1], Cláudia Soares Rodrigues[2], Eliasz Engelhardt[1], Jerson Laks[1]

ABSTRACT

Objective: The aim of this study is to evaluate the survival rate in a cohort of Parkinson's disease patients with and without depression. **Methods:** A total of 53 Parkinson's disease subjects were followed up from 2003-2008 and 21 were diagnosed as depressed. Mean time of follow up was 3.8 (SD 95% = 1.5) years for all the sample and there was no significant difference in mean time of follow up between depressed and nondepressed Parkinson's disease patients. Survival curves rates were fitted using the Kaplan-Meier method. In order to compare survival probabilities according to the selected covariables the Log-Rank test was used. Multivariate analysis with Cox regression was performed aiming at estimating the effect of predictive covariables on the survival. **Results:** The cumulative global survival of this sample was 83% with nine deaths at the end of the study – five in the depressed and four in the nondepressed group, and 55.6% died in the first year of observation, and none died at the fourth and fifth year of follow up. **Conclusion:** Our finding point toward incremental death risk in depressed Parkinson's disease patients.

Keywords
Parkinson's disease, depression, mortality.

RESUMO

Objetivo: O objetivo deste estudo é avaliar a taxa de mortalidade em uma coorte de parkinsonianos com e sem depressão. **Métodos:** O total de 53 pacientes com doença de Parkinson foi acompanhado de 2003 a 2008, e 21 deles foram avaliados com depressão. O tempo médio de doença foi de 3,8 (DP 95% = 1,5) anos para toda a amostra e não houve diferença significativa entre os parkinsonianos, com e sem depressão, acompanhados durante esse período. Curvas de sobrevida foram obtidas utilizando-se o método de Kaplan-Meier. A fim de comparar as probabilidades de sobrevivência de acordo com as covariáveis selecionadas, o teste Log-Rank foi usado. A análise multivariada com regressão de Cox foi realizada com o objetivo de estimar o efeito de covariáveis preditivas sobre a sobrevivência. **Resultados:** A sobrevivência global acumulada dessa amostra foi de 83%, com nove mortes no final do estudo – cinco no grupo com depressão e quatro no grupo sem depressão. Além disso, 55,6% morreram durante o primeiro ano de observação, e nenhum morreu no quarto e quinto ano de acompanhamento. **Conclusão:** Nossos achados indicam um incremento no risco de morte em pacientes com doença de Parkinson e depressão.

Palavras-chave
Doença de Parkinson, depressão, mortalidade.

1 Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brazil.
2 Universidade Estadual do Rio de Janeiro (UERJ), Rio de Janeiro, RJ, Brazil.

Received in
10/19/2013
Approved in
2/4/2013

Address for correspondence: Cláudia Débora Silberman
Rua Barata Ribeiro, 774/407, Copacabana – 22051-000 – Rio de Janeiro, RJ, Brazil
Telephone: (21) 2236-7989
E-mail: silbermanclaudia@gmail.com

INTRODUCTION

Parkinson's disease (PD) is a chronic subcortical neurodegenerative disease which is best diagnosed by motor symptoms and sings. The non motor signs, however, are quite important as they progress contributing to the incapacities that ensue over the course of the disease[1]. Among the non-motor symptoms in PD, depression is highly prevalent with rates around 35%[2].

Several studies have shown that PD exerts a negative impact on the patient's survival, with a risk ranging from 1.5 to 2.9 as compared to the general population[3-8]. Likewise, depression has been reported as an independent variable contributing to increase mortality risk[9]. Indeed, a six-year follow up study with chronic depressed elderly pointed to an incremental mortality risk of 41%[10]. The severity of the depressive symptoms seems to hold a direct relationship with mortality in the elderly[10,11].

Based on these data it would be reasonable to present the hypothesis that PD patients with depression would have a lower survival rate than the PD patients without depression. Conversely a previous review yielded only two studies with conflicting results. The early one did not find an association between depression and survival in PD[12], whereas Hughes *et al.*[13], reported that depressed PD patients presented a 1.64 (CI 1.26-2.99) risk of death as compared to controls. In order to provide more information on this issue, the aim of this study is to evaluate the survival rate in a cohort of PD patients with and without depression.

METHOD

Patients

A consecutive series of PD patients (n = 100) were screened in three neurologic outpatient facilities from January 2003 to April 2006. Patients with dementia or with any other neurological or clinical disorders other than PD were not included in the study, as well as subjects with psychiatric disorders other than depression. Smokers and drug addicts were excluded. Patients using antidepressant medications at baseline or who were taking such medications until three months prior to the inclusion interview were also excluded from the study. In order to evaluate the cognitive status and to exclude dementia the Mini-Mental State Examination (MMSE)[14] and CAMDEX/CAMCOG (Cambridge Examination for Mental Disorders of the Elderly[15] (required score above 80) were used. We employed a validated Brazilian version of the CAMCOG[16].

Neurological examination

All the patients were examined by a neurologist for a detailed diagnosis of PD according to the United Kingdom Parkinson's Disease Society Brain Bank (UK-PDS-BB) criteria[17]. PD staging and severity was ascertained using the Hoehn and Yahr stages (HY)[18]. This scale is used when patients were on the on period. All the patients had a normal CT scan. A psychiatrist evaluated the patients to determine a diagnosis of depression according to the DSM-IV criteria[19] and its severity as measured by the Montgomery Asberg Depression Rating Scale (MADRS)[20] and the Beck Depression Inventory (BECK)[21,22].

With the use of standard clinical criteria, such as the UK Parkinson's disease brain bank criteria, accuracy of a clinical diagnosis of the disease can be improved significantly; however, up to 10% of the patients diagnosed with the disease in life will still have to be reclassified at post-mortem examination[23]. Diagnostic sensitivity and specificity of these criteria have been estimated as 98.6% and 91.1% respectively[24].

Study design

The study started as a cross-sectional study aiming to compare frontal functions in depressed and nondepressed PD. The methodology of this study is described elsewhere[25].

In 2008, the whole population was reassessed. Data on death and respective causes were collected in two complementary ways: an active search via telephone contact plus information search in the Mortality Information System, a database held by the Coordination of Vital Data of the Health Department of the State of Rio de Janeiro, Brazil. The data were captured by certificates reports from 2003 to 2007. To prevent mistakes regarding the presence of homonyms the data were compared with the information recorded in our own databank of the cohort.

In most cases, the cause of death was not specified. Some causes identified were from cardiovascular causes (like Acute Myocardial Infarction), infectious (pneumonia and septicemia) and pulmonary (obstructive pulmonary disease).

Ethics

The study was approved by the local Ethics Committee and all the patients signed the informed consent prior to any procedure. A written permission was issued by the Health State Department to access the mortality database.

Statistical analysis

Descriptive analysis of patient characteristics and initial cognitive tests were carried out to obtain frequency distributions, and the means and standard deviations. The date of inclusion into the cohort was considered as the baseline for the survival analysis of each patient. The primary endpoint was all causes mortality during the follow-up period and survival time was calculated since the cohort inclusion until the death date. All individuals who did not have death registry or who could not be contacted by telephone were censored at the end of data collection period. Follow-up losses were not considered in this study as analyses were based on secondary data, phone contact, and on clinical visits.

The annual mortality rates and survival rates were estimated using the Kaplan Meier method[26]. In order to compare

survival probabilities according to the selected covariables the Log-rank test was used. Next, a multivariate analysis with Cox regression was performed aiming at estimating the effect of predictive covariables on the survival. Statistical analysis was performed using SPSS17.0 statistic software (SPSS Inc., USA).

RESULTS

A total of 53 PD subjects met the inclusion criteria for the study and 21 were diagnosed as depressed at the psychiatric examination. Baseline characteristics of the patients with and without depression are shown in table 1. The severity of PD by Hohen an Yahr stages and the presence of depression are shown in table 2.

Mean (standard deviation) time of follow up was 3.8 (1.5) years for all the sample and there was no significant difference in mean time of follow up between depressed and nondepressed PD patients. The cumulative global survival of this sample was 83% with nine deaths at the end of the study – five in the depressed and four in the nondepressed group (Table 3). Of note, 55.6% died in the first year of observation, and none died at the fourth and fifth year of follow up (Table 4).

The depressed group shows a higher rate of mortality than the nondepressed one as shown in figure 1.

Table 5 shows that the Hazard Ratio (HR) for deaths of PD patients with depression is 2.17 higher than for the nondepressed group, although not statistically significant (p = 0.15). Additionally, the better the cognitive status, the lower the death risk is (HR = 0.98), again not statistically significant (p = 0.495).

As age and cognitive status are considered confounding variables for examining mortality risk in patients with PD and depression, an analysis was run controlling for these covariables. In this analysis, the mortality HR reached 2.42 in depressed patients (p = 0.103).

Table 1. Sociodemographic and clinical profile of PD patients with and without depression

	Depressed (n = 21) Mean (standard deviation)	Nondepressed (n = 32) Mean (standard-deviation)	p-value*
Age	68.38 (10.39)	68.55 (8.40)	0.716
Education (years)	2.24 (1.57)	2.38 (1.69)	0.860
Duration of disease (years)	7.76 (5.00)	5.41 (2.81)	0.113
MMSE**	22.15 (6.73)	22.66 (7.48)	0.534
CAMCOG***	58.05 (36.40)	70.97 (27.56)	0.217
MADRS****	11.57 (9.46)	3.21 (3.79)	0.001
BDI*****	18.95 (11.69)	7.38 (5.24)	p < 0.001

* Mann-Whitney U test; ** MMSE: Mini-Mental State Examination; *** CAMCOG: Cambridge Cognitive Examination; **** MADRS: Montgomery Asberg Depression Scale; ***** BDI: Beck Depression Inventory.

Table 2. Severity by Hohen and Yahr stages in patients with or without depression

	Depression		Total
	No	Yes	
1	9 19.6%	1 2.2%	10 21.7%
2	6 13.0%	3 6.5%	9 19.6%
2.5	9 19.6%	6 13%	15 32.6%
3	4 8.7%	5 10.9%	9 19.6%
4		3 6.5%	3 6.5%
Total	28 60.9%	18 39.1%	46 100.0%

Table 3. Distribution of deaths in the sample with and without depression

			Deaths		Total
			No	Yes	
Depression	No	N	28	4	32
		%	87.5%	12.5%	100%
	Yes	N	16	5	21
		%	76.2%	23.8%	100%
Total		N	44	9	53
		%	83.0%	17.0%	100%

Table 4. Annual frequency and mortality rates

	Frequency	%	Cummulative %	Population at risk	Mortality rate
Death- 1st year	5	55.6	55.6	53	0.09434
Death- 2nd year	2	22.2	77.8	47	0.042553
Death- 3rd year	2	22.2	100	45	0.044444
Total	9	100.0			

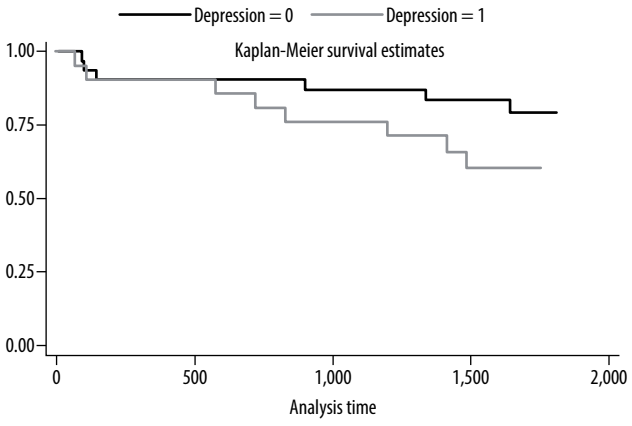

Figure 1. Kaplan-Meier survival estimates.

Table 5. Cox regression adjusted only by depression or by depression + age + MEEM

Depression only					
Variable	HR	SD	Z	p value	CI 95%
Depression	2.17	1.17	1.43	0.152	0.751- 6.255
Depression + MEEM + age					
Variable	HR	SD	Z	P value	CI 95%
Depression	2.42	1.31	1.63	0.103	0.837- 7.003
MMSE	0.98	0.03	-0.68	0.495	0.917-1.043
Age	1.04	0.03	1.15	0.249	0.976-1.100

MMSE: Mini-Mental State Examination; HR: Hazard Ratio; SD: standard deviation; CI: confidence interval; Z: Z statistical test.

DISCUSSION

The influence of depression on mortality of PD patients is still a matter of debate. PD alone was associated to a threefold increase of the mortality risk compared to non PD in elderly populations[3-8]. On the other hand, another study which observed a chronically depressed elderly population for 6 years found a 41% increase in the mortality rate compared to non-depressed subjects[10]. To the best of our knowledge, this is the first Brazilian study and the third study in the world over the last 18 years to address mortality rates in PD comparing depressed and nondepressed patients. Albeit not statistically significant, the HR for mortality in depressed PD patients was 2.45 times higher than in nondepressed ones when we controlled for cognitive status. Another study found that the HR for mortality in depressed PD patients was 2.66 (95% CI: 1.59-4.44) over 11 years of observation[13]. Despite the differences in the two studies, such as the presence of a control group, the sample size, and time of follow up, all these results are pointing to the same direction.

Of note in our study, half of the deaths occurred in the first year of observation (55.6%), a high rate which might be also associated with the higher age of patients, duration of disease, and worse economic and cultural status of the population[27,28]. A recent study in a large elderly male population[29] has presented convincing data with regards to the direct relationship between mortality and severity of depressive symptoms (dose-response relationship) even when controlled by factors as health status and age. Depression may increase mortality risk by a number of reasons. Firstly, comorbidity with clinical disorders is higher and depression also complicates the course of these disorders[30]. Secondly, a series of pathophysiological cascades with cytokines (*e.g.*, IL6, alpha TNF) and lower levels of protective factors (*e.g.*, BDNF, IGF1)[31] are triggered by depressive states. Inflammatory states are then a possible cause of higher mortality and neurodegeneration. All these factors also are present in PD. So, it remains to be studied the impact of having depression when a neurodegenerative disorder is already diagnosed.

There are some limitations in our study which warrant some comments. The first one is the small sample size which possibly impacted in the lack of statistical significance. The absence of a group without PD and depression precluded a better study of the interaction of the two disease and its association with mortality. Moreover, as patients were not actively followed, the presence of follow-up and information biases could not be excluded.

In most cases, the cause of death was not specified (there is a serious problem with the completion of death certificates in Brazil). Some causes identified were from cardiovascular causes (like Acute Myocardial Infarction), infectious (pneumonia and septicemia) and pulmonary (obstructive pulmonary disease).

CONCLUSION

In summary, our finding points towards an incremental death risk in depressed PD patients. Further studies with larger samples are warranted to dissect whether this risk is present and irrespective of other variables, such as depression symptom severity and staging of PD, as well as whether treatment of depression is able to lower this risk.

INDIVIDUAL CONTRIBUTIONS

Cláudia Débora Silberman – Principal investigator. Contributed to conception, design analysis and interpretation of the data. Also contributed to drafting the article, revising it critically and approval of the final version to be published.
Cláudia Soares Rodrigues – Responsible for all statistical calculations. She also contributed to: analysis and interpretation of data, revising the article critically; and had given the final approval of the version to be published.
Eliasz Engelhardt – Contributed to conception, analysis and interpretation of the data; revising it critically for important intellectual content; and had given the final approval of the version to be published.
Jerson Laks – Contributed to conception, design analysis and interpretation of the data. He also contributed to drafting the article, revising it critically and approval of the final version to be published.

ACKNOWLEDGMENTS

To the Conselho Nacional de Pesquisa (CNPq) for supporting Jerson Laks, who is a Researcher 2 of CNPq.

CONFLICTS OF INTEREST

The authors declare no conflict of interest concerning the work presented here.

REFERENCES

1. Hely MA, Morris JGL, Reid WGJ, Trafficante R. Sydney multicenter study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. Mov Disord. 2005;20:190-9.
2. Reijnders JS, Ehrt U, Weber WE, Aarsland D, Leentjens AF. A systematic review of prevalence studies of depression in Parkinson's disease. Mov Disord. 2008;23:183-9.
3. Berger K, Breteler MM, Helmer C, Inzitari D, Fratiglioni L, Trenkwalder C, et al. Prognosis with Parkinson's disease in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology. 2000;54:S24-7.
4. Parashos SA, Maraganore DM, O'Brien PC, Rocca WA. Medical services utilization and prognosis in Parkinson disease: a population-based study. Mayo Clin. 2002;77:918-25.
5. Fall PA, Saleh A, Fredrickson M, Olsson JE, Granérus AK. Survival time, mortality, and cause of death in elderly patients with Parkinson's disease: a 9-year follow-up. Mov Disord. 2003;18:1312-6.
6. Chen H, Zhang SM, Schwarzschild MA, Hernan MA, Ascherio A. Survival of Parkinson's disease patients in a large prospective cohort of male health professionals. Mov Disord. 2006;21:1002-7.
7. D'Amelio M, Ragonese P, Morgante L, Reggio A, Callari G, Salemi G, et al. Long-term survival of Parkinson's disease: a population-based study. J Neurol. 2006;253:33-7.
8. Driver JA. Parkinson disease and risk of mortality: a prospective comorbidity-matched cohort study. Neurology. 2008;70:1423-30.
9. Wulsin LR, Vaillant GE, Wells VE. A systematic review of the mortality of depression. Psychosom Med. 1999;61:6-17.
10. Schoevers RA, Geerlings MI, Deeg DJ, Holwerda TJ, Jonker C, Beekman AT. Depression and excess mortality: evidence for a dose response relation in community living elderly. International J Geriatr Psychiatry. 2009;24:169-76.
11. Schulz R, Beach SR, Ives DG, Martire LM, Ariyo AA, Kop WJ. Association between depression and mortality in older adults. The cardiovascular health study. Arch Intern Med. 2000;160:1761-8.
12. Starkstein SE, Bolduc PL, Mayberg HS, Preziosi TJ, Robinson RG. Cognitive impairments and depression in Parkinson's disease: a follow up study. J Neurol Neurosurg Psychiatry. 1990;53:597-602.
13. Hughes TA, Ross HF, Mindham RH, Spokes EG. Mortality in Parkinson's disease and its association with dementia and depression. Acta Neurol Scand. 2004;110:118-23.
14. Folstein MF, Folstein SE, Mchugh PR. Mini mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189-98.
15. Roth M, Tym E, Mountjoy CQ, Huppert FA, Hendrie H, Verma S, et al. CAMDEX. A standardized instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. Br J Psychiatry. 1986;149:698-709.
16. Bottino CMC, Almeida OP, Tamai S, Forlenza OV, Scalco MZ, Carvalho IAM. Entrevista estruturada para o diagnóstico de transtornos mentais em idosos – CAMDEX – The Cambridge examination for mental disorders of the elderly. Brazilian version (translated and adapted on behalf of the editors). Cambridge: Cambridge University Press; 1999.
17. De Rijk MC, Rocca WA, Anderson DW, Melcon MO, Breteler MM, Maraganore DM. A population perspective on diagnostic criteria for Parkinson's disease. Neurology. 1997;48:1277-81.
18. Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. Neurology. 1967;17:427-42.
19. American Psychiatric Association. Task force on nomenclature and statistics. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, D.C: American Psychiatric Association; 1994.
20. Montgomery SA, Asberg M. New depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-9.
21. Dratcu L, Da Costa Ribeiro L, Calil HM. Depression assessment in Brazil. The first application of the Montgomery-Asberg depression rating scale. Br J Psychiatry. 1987;150:797-800.
22. Goreinstein C, Andrade L. Validation of a Portuguese version of the Beck depression inventory and the state-trait anxiety inventory in Brazilian subjects. Braz J Med Biol Res. 1996;29:453-7.
23. Hughes AJ, Daniel SE, Lees AJ. Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease. Neurology. 2001;57:1497-9.
24. Hughes AJ, Daniel SE, Ben Shlomo Y, Lees AJ. The accuracy of diagnosis of Parkinsonian syndromes in a specialist movement disorder service. Brain. 2002;125:861-70.
25. Silberman CD, Laks J, Capitão CF, Rodrigues CS, Moreira I, Vasconcellos LF, et al. Frontal functions in depressed and nondepressed Parkinson's disease patients: impact of severity stages. Psychiatry Res. 2007;149:285-9.
26. Armitage P, Berry G. Survival analysis. In: Armitage P, Berry G, editors. Statistical methods in medical research. 2nd ed. London: Blackwell Scientific Publications; 1988. p. 421-39.
27. Hely MA, Reid WGJ, Adena MA, Halliday GM, Morris JGL. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord. 2005;23:837-44.
28. Marras C, McDermott MP, Rochon PA, Tanner CM, Naglie G, Rudolph A, et al. Survival in Parkinson disease: thirteen-year follow-up of the DATATOP cohort. Neurology. 2005;64:87-93.
29. Almeida OP, Alfonso H, Hankey GJ, Flicker L. Depression, antidepressant use and mortality in later life: the health in men study. PLoS One. 2010;5:11266.
30. Laks J, Engelhardt E. Reports in pharmacological treatments in geriatric psychiatry: is there anything new or just adding to old evidence? Curr Opin Psychiatry. 2008;21:562-7.
31. Laks J, Engelhardt E. Peculiarities of geriatric psychiatry: a focus on aging and depression. CNS Neurosc Ther. 2010;16:374-9.