Article

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Dementia in Parkinson's disease

A Brazilian sample

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ABSTRACT

To determine the prevalence of dementia associated with Parkinson's disease (PD-D) in a Brazilian sample adopting clinical and diagnostic procedures recommended by the Movement Disorders Society (MDS). Sixty-seven patients were consecutively submitted to neurological, neuropsychological and functional examinations. PD-D was established according to MDS clinical criteria (Level II) and clinical procedures for PD-D (Level I) and prevalence rate was compared between the levels adopted. Ten patients (14.9%) were diagnosed as demented by Level I criteria whereas sixteen (23.8%) were diagnosed based on Level II criteria. Level I criteria had low sensitivity in detecting PD-D (31.25%), but greater specificity (90.19). The PD-D group had significantly worse performance on all neuropsychological tests, were older ($p<0.001$), had an older age of onset ofdisease ($p<0.01$), had lower educational level ($p<0.02$) and had higher scores on functional scales. Current age ($p=0.046$) and Hoehn & Yahr score ($p=0.048$) were predictors for developing PD-D.

Key words: Parkinson's disease, Parkinson's disease dementia, neuropsychological evaluation.

Prevalência da demência associada à doença de Parkinson: uma amostra brasileira

RESUMO

Determinar a prevalência de demência associada à doença de Parkinson (D-DP) em uma amostra brasileira, adotando os procedimentos diagnósticos e clínicos recomendados pela Movement Disorders Society (MDS). Sessenta e sete pacientes foram submetidos à avaliação neurológica, neuropsicológica e funcional. D-DP foi estabelecida de acordo com os procedimentos (Nível I) e critérios clínicos propostos pela MDS (Nível II) e a prevalência de D-DP foi comparada entre os níveis adotados. A prevalência de D-DP encontrada pelo Nível I e II, foi de 14,9% e 23,8%, respectivamente. O Nível I apresentou baixa sensibilidade em detectar D-DP (31,25%), porém, mostrou alta especificidade (90,19%). O grupo D-DP teve desempenho significativamente inferior em todas tarefas neuropsicológicas, eram mais velhos ($p<0,001$), mais velhos ao início da doença ($p<0,01$), menos escolarizados ($p<0,02$) e elevados escores nas tarefas funcionais. Idade atual ($p=0,046$) e escore no Hoehn & Yahr ($p=0,048$) foram apontados como preditores do desenvolvimento de D-DP.

Palavras-Chave: doença de Parkinson, demência associada à doença de Parkinson, avaliação neuropsicológica.

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Despite the fact that Parkinson's disease (PD) is known as a motor disease, it has been increasingly recognized as also consisting of cognitive[1,2] deficits are common even in early and newly diagnosed PD[3].

Parkinson's disease patients have an almost sixfold increased risk of developing dementia compared to healthy controls and 3-4% of dementia cases in the general population are due to PD[2]. Risk factors for development of dementia associated with Parkinson's disease (PD-D) include in-

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creasing age, older age at onset of disease, longer disease duration, severity of parkinsonism, male gender and presence of psychiatric symptoms[4].

The incidence and prevalence rates of PD-D are controversial, and it could be attributed to differing methods used to define PD-D[5] and to the fact that there is a lack of specific criteria for clinical diagnosis of PD-D. In an effort to minimize the wide variations of PD-D prevalence, the Movement Disorder Society Task Force on Dementia in Parkinson's Disease (MDS) published clinical diagnostic criteria for "probable" and "possible" PD-D[5]. They also developed diagnostic procedures for PD-D[6] with two levels of assessment. In diagnostic procedure Level I, a brief screening tool is conducted by a physician to diagnose PD-D, whereas Level II diagnosis consists of an extensive neuropsychological battery of tests that could determine severity of cognitive impairments. Because these diagnostic procedures for PD-D have been proposed recently, their sensitivity and specificity in detecting PD-D are still unknown.

The aim of this study was to compare the prevalence of dementia associated with Parkinson's disease using clinical[5] and diagnostic procedures[6] and the criteria recommended by the MDS task force for PD-D. Furthermore, we wanted to determine the prevalence rates and predictors of PD-D in a Brazilian sample.

METHOD

Ninety patients who fulfilled our inclusion criteria and provided written informed consent (by their relatives in PD-D or in illiterate patients) were enrolled in the study. The study was approved by the local ethics committee. All patients were consecutively recruited from the Neurology Service of Hospital Santa Marcelina in São Paulo. All patients fulfilled criteria for Parkinson's disease according to the United Kingdom Parkinson's Disease Society Brain Bank[7]. PD patients were submitted to demographic and neurological evaluations. Demographic data included age at onset of disease, duration of disease (determined by years since onset of disease), drug treatment and years of schooling.

Exclusion criteria included major depression (measured by beck depression inventory (BDI) score >19)[8], vascular events, concomitant severe or uncontrolled chronic illness, pharmacological effect (e.g., dopamine antagonists), uncorrected visual or hearing impairment and refusal to participate in the study. Illiteracy was not included in the exclusion criteria. Moreover, all patients who completed at least 75% of neuropsychological battery were included.

Functional assessment

Activities of daily living (ADL) were evaluated using Disability Assessment of Dementia (DAD)[9] and Pill Questionnaire[6] scores. The DAD scale evaluates the patient's capacity to perform basic ADL (dressing, hygiene, continence and eating), instrumental activities (meal preparation, telephoning, housework, taking care of finances and correspondences, going on an outing, taking medications and being able to stay safe at home) and leisure activities within the past four weeks. The DAD scale also investigates the degree of complexity of behavior or independence (initiation, planning, organization and effective action) by the patient. The Pill Questionnaire was proposed as a diagnostic procedure to assess functional impairment by the MDS task force on PD-D[6] and refers to questions asked to the patient and their caregiver about the ability to independently organize their daily distribution of antiparkinsonian medications.

The neurological assessment integrated two clinical scales to determine the severity of PD: Hoehn & Yahr staging[10] and Unified Parkinson Disease Rating Scale (UPDRS)[11]. Functional disability was evaluated by the Schwab and England scale[12].

Neuropsychological assessment

The neuropsychological assessment battery included screening tools (Mini Mental State Examination (MMSE) and Beck Depression Inventary)[13,14], short-term and working memory for verbal and spatial materials (Digit span[15], Corsi blocks tapping, forward span and backward span[16]), episodic memory (Logical Memory, Visual Reproduction[17], Figure Complex of Rey[18] and Rey Auditory Verbal Learning tests (RAVLT)[19]), executive functions (Trail Making part B[20], Frontal Assessment Battery (FAB)[21], Phonemic Fluency verbal and FAS[22]), attention (Trail Making part A)[23] and semantic fluency verbal[24]. To avoid fatigue in the PD patients, neuropsychological assessment was conducted over two visits, each one lasting approximately one and a half hours in duration. Due to dyskinesia or illiteracy, some patients were unable to complete all tests.

Procedure

Each patient was submitted to neurological and neuropsychological assessments by independent raters who were blind to the results obtained in each other's evaluation. The results from the neuropsychological tests were used to subdivide the sample using both diagnostic procedures (Level I)[6] and clinical criteria (Level II)[5] recommended by the MDS task force for PD-D.

Classification of the sample using clinical diagnostic criteria for PD-D (Level II)

A diagnosis of PD-D was established if: [A] dementia developed after the diagnosis of idiopathic PD; [B] there

was a presence of cognitive deficits in at least two cognitive domains (including memory impairment); [C] cognitive impairment was severe enough to affect premorbid level; [D] deficits were severe enough to impair daily life independent of the impairment explained by motor or autonomic symptoms and [E] the cognitive and behavioral symptoms were not better explained by other conditions or diseases. The patient was classified with impaired cognition if performance scores were lower than 1.5 SD below the Brazilian normative data (available to MMSE, FAB, RAVLT, semantic and phonemic fluency verbal tests) in at least two cognitive domains, being that abnormal performance in a single test represents cognitive function impairment.

Classification of the sample using diagnostic procedures for DP-D (Level I)

A diagnosis of PD-D was given if PD developed prior to the onset of dementia, MMSE <26, cognitive impairment impacted daily living (measured by the Pill Questionnaire), and patients had impairment in at least two of following tests: seven backwards, pentagons and word recall (MMSE subtests) and lexical fluency.

Data analysis

Differences in demographic and clinical characteristics between PD and PD-D groups were analyzed with descriptive statistics. The Mann-Whitney test was used to compare performance between groups on cognitive tests.

Logistic regression analyses were used to identify age, Hoehn & Yahr scores and years of schooling as predictors of developing PD-D. All analyses were performed using Statistics 6.0 software, and p values were calculated at the 0.05 significance level.

RESULTS

From the ninety PD patients consecutively enrolled in this study, twenty-three patients (25%) was excluded because they fulfilled depression criteria or had difficulties in filling out at least 75% of the cognitive assessment due to illiteracy or dyskinesia. Demographics, clinical characteristics and cognitive performance on neuropsychological tests from the overall sample and from PD or PD-D subgroups defined by diagnostic procedures and clinical criteria (Levels I and II) for PD-D are shown in Table.

We found that 23.8% (16 patients) of the demented patients met the clinical MDS diagnostic criteria for PD-D. The PD-D group had lower number of years of schooling (U=189.00, p=0.001), was older (U=189.50, p=0.001) and was older at the onset of disease (U=191.00, p=0.001). Patients in this group also showed more severe disease (Hoehn & Yahr, U=276.00, p=0.05) and lower independence on activities of daily living (Schwab and England scale, U=230.00, p=0.01). In a neuropsychological assessment, the PD-D group had significantly lower performance on several measures, including the screening tool (MMSE, U=66.50, p<0.01) and verbal episodic memory tests (Logical Memory and RAVLT) for both immediate recall (U=113.00, U=219.50, respectively; p's<0.01) and delayed recall (U=97.50; U=167.50; p's<0.01). The PD-D group also had poorer performance on visual episodic memory tests (Figure Complex of Rey and Visual Reproduction) on immediate recall (U=169.50, U=192.50, respectively; p's<0.001), delayed recall (U=255.50; U=105.00; p's<0.001), backwards spatial span (Corsi, U=186.00, p=0.002) and constructive praxis (copy of Figure Complex of Rey, U=54.50; p=0.03). Poorer performances on cognitive tests that involved speed processing (Stroop card I, U=49.00, p<0.01) and executive functions (Trail Making part B, U=32.50, p=0.03; Stroop card II, U=133.00, p=0.01) were also observed in the PD-D group.

The comparison between Level I and II diagnostic criteria showed that whereas clinical diagnostic criteria (Level II) found a 23.8% (16 patients) PD-D prevalence rate, Level I diagnostic procedures found PD-D in 14.9% (10 patients). Compared to PD patients without dementia as diagnosed by Level I criteria, the PD-D sample had poorer scores on the UPDRS factor I and II (U=131.00, U=138.50, respectively, p's<0.02) and on the MMSE (U=83.50; p<0.01). Considering that Level I diagnostic criteria involves some items from the MMSE that can be influenced by the number of years of schooling, we reanalyzed the data, taking into account educational level cutoff scores from the MMSE subtests (impairment on Serial 7's changed from 2 incorrect answers to 3, impairment on 3-word recall changed from 2 to 1 and missing word and drawing pentagons had no score alteration) and found that 49.2% (n=28) patients who were cognitively intact were reclassified as cognitively impaired. After reanalyzing the data with Brazilian cutoffs, we observed that the prevalence of dementia remained the same. The main reason that the prevalence of PD-D was unaltered may be that 8 patients who could be classified as demented were not classified as such because they did not have ADL impairment as measured by the Pill Questionnaire. However, all these patients had ADL impairment according to the DAD scale.

Level I criteria had low sensitivity in detecting PD-D (31.25%), greater specificity (90.19%) and positive and negative predictive values of 50% and 82.45%, respectively.

Logistic regression analysis found that current age (p=0.046) and Hoehn & Yahr score (p=0.048) were predictors of developing of dementia associated with Parkinson's disease.

Table. Demographical and clinical data of the PD sample and performance on neuropsychological evaluation of PD and PD-D subgroups (Median±standard deviation).

		Diagnostic procedures for PD-D		Clinical diagnostic criteria for PD-D		
	PD patients (n=67)	PD NorCog (n=57)	PD-D (n=10)	PD NorCog (n= 51)	PD-D (n=16)	P value*
Age, years	66.97±11.71*	65.60±11.55	74.8±9.77	64.37±11.24	75.25±9.27*	0.04
Female (%)	50.76	45.61	80	41.17	81.25	
Years of schooling	4.72±3.60	5.35±3.50	1.10±1.37	5.51±3.72	2.18±1.42*	0.001
Illiterate (n)	6	1	5	4	2	
Age at onset of disease	61.36±12.78	59.91±12.55	69.60±11.32	58.57±11.98	70.25±11.34*	0.001
Time of PD, years	6.08±4.90	6.36±5.04	4.50±3.87	6.32±4.78	3.75±3.33	0.28
UPDRS - Factor I	2.65±2.21	2.30±1.72	4.78±3.49	2.28±1.54	14.25±8.01	0.02
UPDRS - Factor II	12.81±6.97	12.20±6.92	16.44±6.48	12.32±6.60	27.62±12.92	0.03
UPDRS - Factor III	27.24±12.61	27.33±13.06	26.67±10.09	27.11±12.64	2.75±3.53	0.96
UPDRS - Factor IV	2.90±3.07	3.02±2.94	2.22±3.87	2.96±2.93	48.25±21.81	0.18
UPDRS - Total	45.79±20,28	45.09±20.53	50±19.29	44.96±19.91	66.25±18.57	0.46
Hoehn & Yahr	2.55±0.67	2.54±0.70	2.60±0.52	2.45±0.68	2.87±0.56	0.01
Scwhab and England	75.71±17.66	76.85±17.79	68.9±16.1	78.94±16.3	66. 25±18.57	0.01
DAD	72.92±6.74	72.92±6.74	66.44±5.59	74.59±4.69	64.37±6.90	0.00008
BDI	9.06±4.46	8.60±4.26	11.70±4.88	8.59±4.74	10.56±3.05	0.11
MMSE	23.28±4.13	24.16±3.40	18.40±4.55	24.70±3.10	18.53±3.58	0.0000
FAB	9.73±3.84	10.41±3.60	6.10±3.14	10.63±3.71	6.80±2.65	0.002
Logical memory immediate recall	13.52±8.96	14.55±9.00	7.44±6.11	16.15±8.80	5.93±3.37	0.0000
Logical memory delayed recall	8.84±8.29	9.74±8.34	3.44±5.72	11.28±8.15	1.68±2.65	0.0000
RAVLT - Σ A1-A5	26.62±9.34	27.41±9.15	21.89±9.62	28.69±8.92	20.00±7.58	0.008
RAVLT - list B	2.77±1.81	2.81±1.91	2.50±1.18	3.08±1.77	1.73±1.57	0.01
RAVLT - immediate recall	4.39±2.83	4.67±2.73	2.9±3.07	4.85±2.91	2.86±1.92	0.01
RAVLT - delayed recall	4.30±2.78	4.57±2.74	2.80±2.62	5.10±2.38	1.66±2.35	0.00006
FCR - copy	27.57±14.99	28.42±15.07	15.67±7.57	28.89±15.25	18.91±10.20	0.03
FCR - immediate recall	10.19±7.09	10.40±7.21	7.17±5.20	11.08±6.97	5.35±6.08	0.04
FCR - delayed recall	4.30±2.78	9.10±6.86	8.83±3.33	10.09±6.29	3.57±6.24	0.01
Visual reproduction - immediate	15.85±10.65	17.10±10.63	7.42±6.29	18.82±10.22	7.35±6.64	0.0002
Visual reproduction - delayed recall	9.19±9.54	10.44±9.67	1.14±1.21	11.57±9.83	2.71±4.51	0.0008
Digit span forward	4.96±1.17	5.08±1.16	4.22±0.97	5.12±1.17	4.5±1.09	0.06
Digit span backward	2.90±1.09	3.03±0.96	2.11±1.53	3.06±1.01	2.43±1.20	0.12
Corsi - forward	3.79±1.06	3.83±1.02	3.50±0.92	3.83±1.08	3.66±0.72	0.39
Corsi - backward	2. 98±1.209	3.16±1.14	1.75±1.66	3.24±1.19	8.18±3.05	0.002
Semantic fluency verbal	11.12±3.53	11.53±3,35	8.55±3.74	12.08±3.14	8.18±3.05	0.000
Phonemic fluency verbal (FAS)	20.83±10.32	21.21±10.22		2.3±9.82	13.08±8.40	0.003
TMT part A	135.30±101.47	127.62±93.82	289.00±171.11	124.19±95.53	202.0±119	0.07
TMT part B	290.78±180.13	286.62±180.74	445.00	258.30±147.86	505.20±243.00	0.03
Stroop card I	26.17±9.97	26.17±9.97	51.66±11.67	23.57±7.79	41.66±11.82	0.0000
Stroop card II	39.86±21.78	39.86±21.78	75.66±29.56	36.02±14.31	62.25±36.04	0.01
Stroop card III	57.78±33.55	57.58±33.55	66.00±19.79	51.42±21.90	82.63±53.53	0.06

Values are mean±SD. *Mann-Whitney U test. PD: Parkinson's disease; PD-D: Parkinson's disease dementia; COG: cognitive; UPDRS:Unified Parkinson Disease Rating Scale; DAD: Disability Alzheimer Disease Scale; BDI: Deck Depression Inventory; MMSE: Mini Mental Status Exam; FAB: Frontal Assessment Battery; RAVLT: Rey Audictory Learning Test; FCR: Figure Complex of Rey; TMT: Trail Making Test.

DISCUSSION

Our findings showed that the prevalence of PD-D was about 23.8%, corroborating previous studies that place prevalence of PD-D in the PD population at approximately 30%. In addition, older current age and older age at onset of disease, lower educational level and higher scores on the Hoehn & Yahr and Schwab and England scores were associated with PD-D, but only current age and Hoehn & Yahr score predicted the development of PD-D.

Comparison between diagnostic criteria (Level II) and clinical procedures (Level I) for PD-D revealed that Level II had good discrimination in the detection of PD-D, whereas Level I criteria had lower specificity and greater sensitivity as a diagnostic procedure for PD-D. We hypothesized that lower sensitivity with Level I criteria could be related to the adoption of a MMSE cutoff of less than 26. This was confirmed when the data were reanalyzed after taking into account educational level cutoff scores on the MMSE, which revealed that 49% of the sample had an impaired score. This suggests that the MMSE cutoff proposed by MDS Level I criteria could be affected by educational level and not considering educational level leads to a false-negative PD-D diagnosis.

Although the MMSE has been recommended as a useful tool in identifying cognitively impaired patients with PD[6], some studies have called into question its accuracy in detecting cognitive impairments in PD[25]. Therefore, the comparison of cognitive performance of patients with normal cognition according to MMSE to other instruments (SCOPA-COG[26] and MoCA[27]) revelead that MMSE is less insensitive to detect cognitive impairments due to PD.

We also found that few patients had cognitive impairment severe enough to impair the ability to independently organize their daily distribution of antiparkinsonism medication (Pill Questionnaire), which was used as a functional measure proposed by MDS Level I criteria. Twelve of the 20 PD-D subjects (60%) were able to take their antiparkinsonism pills independent of caregiver supervision despite the fact that functional impairment was noted in the DAD scale and only 8 PD-D patients (40%) had functional impairment observed by both the Pill Questionnaire and the DAD scale. For PD patients without dementia, functional impairment was observed by the DAD scale in 5 subjects (8%) who had intact cognitive functioning as measured by the Pill Questionnaire, whereas only 1 patient reported an inability to manage their medications despite having intact functional abilities. Higher difficulties reported in the Pill Questionnaire concerned the ability of the patient to describe their list of drugs and their doses without assistance followed by their ability to take their pills without supervision. In PD-D patients, the sequence of difficulties was the opposite. More patients required a caregiver to help them take their pills than those who had difficulties in describing their pill schedule. Nevertheless, on the DAD scale, we found that the PD-D group had much greater impairments with instrumental ADLs (telephoning, going on an outing, taking care of finances and correspondences and leisure activities) than with basic ADLs (i.e., dressing) in comparison to the non-demented group. However, both groups were able to take their medications. Previous studies found that the association between cognition and ADL depends substantially on instrumental ADLs in PD[28] and the presence of PD-D greatly impairs the ability to perform ADLs[29]. Our results show that the PD-D group had impairment on some cognitive dimensions related to disabilities in ADL, but not in all of them. The initiation to take antiparkinsonism pills remained intact, whereas planning and organizing (measured by correct description of doses and drugs without caregiver supervision) were affected. Thus, it is possible that the ability to remember taking antiparkinsonism pills will be the last domain impaired because taking the medications leads to a reduction of motor symptons. To our knowledge, this is the first study that adopted diagnostic procedures and criteria for PD-D as recommended by the MDS. Our results confirm a recent study[28] that showed that some individuals who are not demented, according to MDS criteria, may have significant disability on the basis of cognitive dysfunction.

As expected, worse performance on all neuropsychological tests was observed in the PD-D group. Moreover, confirming previous studies, we found that age , age at onset of disease, more advanced disease (higher Hoehn & Yahr score) poorer scores on the Schawb and England scale were related to PD-D[9]. Our sample had a low education level overall (4.72±3.60 years), but the PD-D group had a lower education level (2.18±1.42 years). When we conducted a non-linear regression analysis, age and severity of disease (Hoehn & Yahr score), but not years of schooling, appeared as predictors of PD-D.

Although this study demonstrated that prevalence rates of PD-D varied depending on the diagnostic procedure adopted and that clinical characteristics, such as age and severity of disease, are predictors of PD-D, it has some limitations. First, the sample was not representative of the entire population of PD patients. Our sample was only representative of the hospital-based population, which may be subject to a selection bias. Second, although the choice of neuropsychological tests was based on recommendations from the MDS task force[6], some tests were influenced by education level (Phonemic Fluency Verbal - FAS, Stroop Color and Trail Making Tests) and motor impairments (Figure Complex of Rey, Trail

Making Test and Visual Reproduction Test), leading to a possible underperformance by patients in our sample who had a low education level, 9% of which were illiterate. Third, it is important to note that despite multiple predictors considered in the present analyses, we did not assess some neuropsychiatric functions (such as apathy and visual hallucination). On other hand, one of the strengths of this study is that, to our knowledge, ours is the first study to compare the incidence of PD-D according to diagnostic procedures and clinical diagnostic criteria proposed by the MDS. Standardized criteria for dementia and neuropsychological evaluations were performed blind to the neurological assessment.

In conclusion, our results indicate that the Level I MDS diagnostic criteria has low sensitivity and specificity in detecting PD-D in comparison to Level II criteria. Moreover, current age and higher Hoehn & Yahr scores were predictors of PD-D and our findings have implications for patient management and clinical practice. Patients with PD, particularly those with risk factors for developing PD-D, should be regularly submitted to brief cognitive assessment and carefully monitored for progression of dementia.

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