ADDENBROOKE'S COGNITIVE EXAMINATION III: DIAGNOSTIC UTILITY FOR DETECTING MILD COGNITIVE IMPAIRMENT AND DEMENTIA IN PARKINSON'S DISEASE

Data de aceite: 02/05/2023

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ABSTRACT: **Background:** Cognitive deficit in Parkinson's disease (PD) is an important cause of functional disability in these patients and early detection, with sensitive instruments, can contribute to longitudinal monitoring. **Objective:** To investigate the diagnostic accuracy, sensitivity, and specificity of the Addenbrooke's Cognitive Examination-III in patients with PD, using the comprehensive neuropsychological battery as reference method. **Methods:** Cross-sectional, observational, case-control study. Setting: rehabilitation service. A total of 150 patients and 60 healthy controls matched for age, sex, and education. For level I assessment, ACE-III was used. Level II assessment used a comprehensive neuropsychological battery of standardized tests for this population. All patients remained in on-state during the study. The battery's diagnostic accuracy was investigated through the ROC (Receiver Operating Characteristic) analysis. **Results:** The clinical group was divided into three subgroups: normal cognition in Parkinson's disease (NC-PD-16%), mild cognitive impairment due to Parkinson's disease (MCI-PD-69.33%), and dementia due to Parkinson's disease (DPD-14.66%). ACE-III optimal cut-off scores for detecting MCI-PD and D-PD were 85/100 (sensitivity 58.65%, specificity 60%) and 81/100 points (sensitivity 77.27%, specificity 78.33%), respectively. Age was inversely associated with the performance of the scores (totals and domains of the ACE-III), while the level of education had a significantly positive correlation in the performance of these scores. **Conclusions:** ACE-III is a useful battery for assessing the cognitive domains and to differentiate individuals with MCI-PD and D-PD from healthy controls. Future research, in a community setting, is necessary to provide discriminatory capacity of ACE-III in the different severities of dementia.

KEYWORDS: Parkinson's disease; Cognitive Dysfunction; Dementia; Neuropsychological Tests.

EXAME COGNITIVO DE ADDENBROOKE III: UTILIDADE DIAGNÓSTICA PARA DETECTAR COMPROMETIMENTO COGNITIVO LEVE E DEMÊNCIA NA DOENÇA DE PARKINSON

RESUMO: Introdução: O déficit cognitivo na doença de Parkinson (DP) é uma importante causa de incapacidade funcional nesses pacientes e a detecção precoce, com instrumentos sensíveis, pode contribuir para o acompanhamento longitudinal. **Objetivo:** Investigar a acurácia diagnóstica, sensibilidade e especificidade, do Exame Cognitivo de Addenbrooke-II em pacientes com DP, usando a bateria neuropsicológica ampla como método de referência. **Métodos:** Estudo transversal, observacional, caso-controle. Local: serviço de reabilitação. Um total de 150 pacientes e 60 controles saudáveis pareados por idade, sexo e escolaridade. Para avaliação do nível I, foi utilizado ACE-III. A avaliação do nível II utilizou o exame neuropsicológico, com testes padronizados para essa população. Todos os pacientes estavam na fase "on" da medicação. A acurácia diagnóstica da bateria foi investigada por meio da análise do ROC (Receiver Operating Characteristic). **Resultados:** O grupo clínico foi dividido em três subgrupos: cognição normal na DP (CN-DP-16%), comprometimento cognitivo leve devido à DP (CCL-DP-69,33%) e demência devido à DP (D-DP- 14,66%). As notas de corte ideais da ACE-III para detectar CCL-DP e D-PD foram 85/100 (sensibilidade 58,65%, especificidade 60%) e 81/100 pontos (sensibilidade 77,27%, especificidade 78,33%), respectivamente. A idade associou-se inversamente com o desempenho dos escores (totais e domínios da ACE-III), enquanto a faixa de escolaridade apresentou correlação significativamente positiva no desempenho desses escores. **Conclusões:** A ACE-III é uma bateria útil para avaliação de domínios cognitivos e diferenciar indivíduos com CCL-DP e D-DP de controles saudáveis. Pesquisas futuras, em ambiente comunitário, são necessárias para fornecer capacidade discriminatória da ACE-III nos diferentes estágios da demência.

PALAVRAS-CHAVE: Doença de Parkinson; Disfunção Cognitiva; Demência; Testes Neuropsicológicos.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative condition initially described as a movement disorder, characterized by symptoms such as tremor, stiffness, bradykinesia, and postural instability[1]. Since the initial stages of the disease, about 20-30% of patients have some cognitive impairment[2], which is an important cause of functional disability in these patients[3,4].

Part of these cognitive alterations is attributed to a dopamine-dependent dysfunction of the frontostriatal pathways, but there is considerable heterogeneity, as well as the influence of other neurotransmitter systems, including the cholinergic one, which is responsible for the dementia syndrome in PD[5].

In mild cognitive impairment (MCI), the patient may complain of difficulties in complex activities with relative preservation of functionality[6]. Despite being referred to as a single and non-amnestic domain, the criteria for this diagnosis are not well established in the literature, with controversies regarding the definition and characteristics of mild cognitive impairment

in PD (MCI-PD), due to the methodological diversity among the studies[6–8].

Dementia in Parkinson's disease (D-PD) is the most serious manifestation. This condition affects about 24% to 31% of patients, increases death risk, and leads to a reduction in the patients' and caregivers' quality of life, besides causing an increase in institutionalization and in costs[9,10].

Many different instruments can be used to evaluate cognition in PD. The Mini-Mental State Examination (MMSE) was proposed as a screening tool in PD patients[11,12] for its simplicity and wide use in dementias. However, early cognitive changes in executive functions are not detected using the MMSE[11,12]. The Mattis Dementia Rating Scale (MDRS) assesses various cognitive aspects, but its application is longer and requires specialized professionals. The Montreal Cognitive Assessment (MoCA) is a global and brief battery, but it does not provide subscores by cognitive domains.

Addenbrooke's Cognitive Examination

The ACE is a brief cognitive assessment battery, with high sensitivity and specificity for detecting mild stage dementia, not requiring specialized equipment. It was developed in 2000 by a team conducted by John R. Hodges and Germán E. Berríos at Addenbrooke's Hospital, Cambridge, UK[13], as a tool to assess early stages and differentiate subtypes of dementia, such as Alzheimer's Dementia (AD) and Frontal-Temporal Dementia (FTD), Vascular Dementia (VD), Progressive Supranuclear Palsy (PSP), and other parkinsonian syndromes[14–17]. It consists of six cognitive domains, totaling 100 points: orientation (10 points), attention (8 points), memory (35 points), verbal fluency (14 points), language (28 points), and visual-spatial skills (5 points). The points related to the six domains can be calculated separately. The sum of all of them equals the total score. This total score includes the 30 MMSE points, which can also be calculated separately.

ACE-III was developed in 2013, with different versions validated in several countries[18–25]. There is evidence of psychometric property and diagnostic ability to distinguish healthy people from patients with dementia. As in the previous version (ACE-R), ACE-III focuses on five cognitive domains (attention/orientation, memory, verbal fluency, visuospatial ability, and language). The total score is still 100. The runtime is still around 20-30 minutes.

In individuals with PD, a study with the first version of ACE[26] demonstrated 92% sensitivity and 91% specificity with a cut-off score of 83 to detect DPD; however, its sample was small (n = 31, without dementia; n = 13, with dementia). Another study[27], also with a small sample, had a cut-off score of 80, capable of detecting dementia (sensitivity: 74%, specificity: 78.1%). With the same version of the instrument, a cut-off score of 83.5 was shown with better diagnostic accuracy (sensitivity: 87.1%, specificity: 79.7%) in differentiating MCI-PD and 80.5 (sensitivity: 86.9%, specificity: 73.7%) in differentiating D-PD[28].

Regarding the third version of ACE, with a sample consisting only of individuals

with PD, there is just one study for validation and standardization, conducted by Lucza et al.[29], in which the sensitivity and specificity of some versions of Addenbrooke's cognitive examination (ACE, ACE-III and mini-ACE) were compared in 552 individuals with PD. For individuals with level of education between 0-8 and 9-12 years, ACE-III, among the three versions, was the one showing the best discrimination skills for MCI-PD (83.5 [level of education:0-8 years, sensitivity of 93%, and specificity of 64%, AUC=0.733]; 85.5 [level of education 9-12 years, sensitivity of 80%, and specificity of 78%, AUC=0.771]; 88.5 [level of education >12 years, sensitivity of 76%, and specificity of 74%, AUC=0.838]). To detect dementia, ACE-III showed the best diagnostic accuracy in all educational levels.

Thus, studies with ACE-III are more focused on neurological conditions, such as AD, FTD, VD, and atypical parkinsonisms, or even on psychiatric conditions such as schizophrenia[30].

This is the first study carried out in Brazil with the third version of ACE and the first exclusively performed in patients with PD, with the neuropsychological assessment as a reference method, and the use of a comprehensive battery of standardized neuropsychological tests being a strength of this study. This assessment is the gold standard for the diagnosis of mild cognitive impairment and mild dementia.

The aims of this study were to investigate the diagnostic accuracy, sensitivity and specificity of the Addenbrooke's Cognitive Examination, third version (ACE-III), to detect MCI-PD and D-PD, and its ability to differentiate between subgroups of patients, and to correlate them with demographic, clinical data, and neuropsychological tests.

METHODS

Study design

This is an observational, cross-sectional, case-control study.

Participants and recruitment

A total of 150 idiopathic PD patients, according to the clinical diagnosis criteria of the Parkinson's UK Brain Bank, were enrolled in the study. For the diagnosis of MCI-PD, the criteria of the Movement Disorder Society, Level II (2012), were used, based on a broad neuropsychological assessment, with a standard deviation of 1.5 below the mean of the normative value (depending on the test) for age, and educational level being considered a cognitive deficit. According to MDS Level II criteria, impaired performance in 1 test in two separate cognitive domains or in 2 tests in the same cognitive domain means cognitive deficit. Functionality assessment, based on the application of a questionnaire on functional activities and cognitive complaints, was also used to differentiate MCI-PD from D-PD.

These patients were from the neurological rehabilitation program of the SARAH Rehabilitation Hospitals, from the unit of the city of Salvador, Bahia. During their admission,

they were evaluated by a neurologist and physiotherapist before being referred for neuropsychological evaluation. Each patient met the clinical diagnostic criteria for PD[31] and provided the written informed consent according to the approval by the Ethics Committee of the SARAH Rehabilitation Hospitals (57521316.8.0000.0022) and the University of Sao Paulo/Department of Neurology (57521316.8.3001.0065). Participants in the clinical group should be over 40 years of age, with 4 years or more of formal education, with no major psychiatric disorders or history of substance use and/or abuse, cerebrovascular disease, and/or other known conditions that could impair mental status and interfere with cognitive performance. Demographic details are presented in Table 1.

Regarding affective aspects, patients with minimum to light intensity scores in the Beck Depression-BDI and Anxiety-BAI Inventories (less than or equal to 16 in BDI and less than or equal to 15 in BAI) were included.

The clinical group was matched for age, sex, and education to the healthy controls. These participants were patients from other rehabilitation programs (orthopedics) or companions for other patients from the same Hospital, who did not participate in this study, in a rehabilitation program. They were recruited according to the following inclusion criteria: formal education of 4 years or more, questionnaire of functional activities[32] of 0 or 1 (minimum score is 0 and maximum is 30, with the presence of functional impairment being considered from a score of > 5 points), with scores above the median values for education[33], delayed Recall of the Figure Memory Test from the Brief Cognitive Screening Battery (BCSB) greater than or equal to 7 of gross scoring[34,35]. Individuals with neurological or psychiatric disorders, cerebrovascular disease, and substance use/abuse were excluded.

ACE-III

As there is little difference between the revised version and the third version of ACE, except for the design belonging to the visuospatial part, the test was performed in Portuguese, with complementation of this part belonging to ACE-III, since it is different from the revised version. The correction remained as in ACE-R.

The ACE-R version contains items from the MMSE and, therefore, the authors themselves decided to create the ACE-III. It was used in this study in order to have its accuracy in the evaluation of patients with Parkinson's disease.

Neuropsychological, functional, and mood evaluations

Disease severity was assessed using the Hoehn and Yahr - H&Y scale by the same examiner (assessed in the on-phase of medication and collected from the electronic medical records).

Cognitive functions were assessed by a neuropsychologist using a comprehensive tests battery: Digit Span (WMS-R)[36], Corsi Block-Tapping Test[37], Mental Control (WMS-R)[36], Rey's Auditory-Verbal Learning Test – RAVLT[38], Rey Complex Figure – RCF[37], Trail Making

Test, parts A and B - TMT-A and TMT-B[39], Phonemic Verbal Fluency – PVF[39].

These tests were conducted in patients in on-medication phase. To avoid PD patients' fatigue, the neuropsychological assessment was conducted over two sessions, each lasting approximately 90 minutes.

The patients were classified as three subgroups: (1) normal cognition in Parkinson's disease (NC-PD), n = 24; (2) mild cognitive impairment due to Parkinson's disease (MCI-PD), n = 104; (3) dementia due to Parkinson's disease (D-PD), n = 22, according to the guidelines of the Movement Disorder Society – MDS[31,40]. Gross data were converted to Z-score and those with a score of 1.5 standard deviations below the average, for their age and education, in 1 test in two separate cognitive domains or in 2 tests in the same cognitive domain, and preserved functionality, were diagnosed as MCI-PD. For the diagnosis of dementia, loss of functionality and decline were considered (Pfeffer's Functional Activity Questionnaire (FAQ) >5 and/or IQCODE >3.41). The individuals were classified by a professional with experience in cognitive neurology, and who was blinded for the patient's information.

Statistical analysis

Data were analyzed using a statistical technique with the aid of the SPSS software, version 22.0. The variables were analyzed using the Chi-square test, Student's t test, Bonferroni test, ROC analysis, Pearson correlation coefficient, Spearman's rho coefficient, according to the type of data (categorical or continuous) and its distribution.

Demographic data, scores on cognitive evaluations, and other quantitative measures were compared through one-way analysis of variance (ANOVA) with Bonferroni's post hoc comparisons.

Pearson's correlation coefficients were used among the continuous variables, such as performance on ACE-III with other cognitive tests, as well as between ACE-III scores and clinical (disease progression and severity) and functional data (FAQ and IQCODE scales scores). The Spearman correlation coefficient, non-parametric correlation, was used for ordinal variables, such as the H&Y scale.

The battery's diagnostic accuracy was investigated through the analysis of the ROC (Receiver Operating Characteristic), 95% CI, curves to check the sensitivity and specificity of the cut-off points (total and domains cut-off scores of the ACE-III), to distinguish between groups of participants (healthy controls vs. MCI-PD and healthy controls vs. D-PD). A cut-off score was identified based on high sensitivity and specificity. The best cut-off point was chosen to balance sensitivity and specificity, identifying the point on the curve closest to point (0.1). In the ROC curve analysis, the groups were combined to estimate the area under the curve (AUC) used to discriminate non-pathological from pathological groups. An AUC between 0.9 and 1.0 was considered "excellent" accuracy; 0.8 to 0.9, "good"; 0.7 to 0.89, "not good"; and 0.6 to 0.79, "worthless"[41]. Diagnostic accuracy was also evaluated through the levels of education (4-9, 10–12 and >= 13 years).

The p-significance value was less than 0.05.

RESULTS

Demographic and clinical profile

A total of 150 patients and 60 healthy controls were recruited for this study.

As it can be seen in Table 1, there was no statistically significant difference between the groups (total clinical and control) in relation to age (t = 0.1942, p = 0.84), years of formal education (t = 1. 1003, p = 0.2725), and sex (χ2 = 0.7046, p = 0.401). In clinical measures of mood and anxiety, as well as in the functional measures, a higher score was observed, that is, a worse result, in the clinical group. Regarding the severity of motor symptoms, there was a higher proportion of patients in stages I and II of the H&Y scale, that is, with less severe disease. This table also illustrates the comparison of ACE-III scores and subscores between these two groups (total clinical and control). There were statistically significant differences in the mean scores of the total ACE-III score (t= -3.1861, p = 0.0017), and in its attention/orientation domains (t = -3.1886, p = 0.0017), memory (t = -2.9926, p = 0.0031), and visuospatial component (t = -2.5188, p = 0.0125).

N= 210	NC-PD (n=24)	MCI-PD (n=104)	D-PD (n=22)	Control Group (n=60)	p value					
					D-PD vs MCI-PD	D-PD vs Control	MCI-PD vs Control	NC-PD vs MCI-PD	NC-PD vs Control	NC-PD vs D-PD
Sex n (%)										
Male	15(62.50%)	78(75%)	11(50%)	38(63.33%)	0.019*	2.75	0.114	0.216	0.943	0.393[b]
Age, years	59.50(8.94)	63.90(8.44)	66.50(9.24)	63.32(9.04)	1.000	0.877	1.000	0.165	0.436	0.044*[a]
Education, years	12.21(4.11)	11.05(3.83)	9.68(4.44)	10.38(3.51)	0.786	1.000	1.000	1.000	0.303	1.000[a]
Disease duration, years	5.58(4.00)	6.69(4.79)	7.32(4.92)	-	1.000	-	-	0.895	-	0.637[a]
Hoehn & Yahr Scale (%)				-	0.005**	-	-	0.023*	-	<0.0001***[a]
I-II	20(13.33%)	59(39.33%)	7(4.66%)	-	0.034*	-	-	0.016*	-	<0.0001***[b]
III-IV	4(2.66%)	45(30%)	15(10%)	-	-	-	-	-	-	-
BDI	4.63(3.88)	5.75(4.37)	8.14(4.23)	0.68(1.63)	0.041*	0.000***	0.000***	1.000	0.000***	0.010*[a]
BAI	2.29(1.68)	3.02(3.06)	4.59(3.67)	0.20(0.51)	0.054	0.000***	0.000***	1.000	0.005**	0.015*[a]
FAQ	0.83(1.31)	2.02(1.88)	7.23(4.68)	0.27(0.48)	0.000***	0.000***	0.000***	0.072	1.000	<0.0001***[a]
IQCODE	3.08(0.17)	3.32(0.43)	4.35(0.87)	3.13(0.23)	0.000***	0.000***	0.034*	0.077	1.000	<0.0001***[a]

N = 210	Clinical Group (n = 150)	Control Group (n = 60)	P value
Sex (%)			

Male	104	38 (63.33%)	0.401[b]
Age, years	63.58 (8.81)	63.32 (9.04)	0.8462[a]
Level of education, years	11.03 (4.00)	10.38 (3.51)	0.2725[a]
Length of disease (years)	6.61 (4.69)	-	-
Hoehn & Yahr scale (%)			
Stages I-II	86 (57.33%)	-	-
Stage III	64 (42.67%)	-	-
BDI	5.92 (4.37)	0.68 (1.63)	<0.0001 *** a
BAI	3.13 (3.04)	0.20 (0.51)	<0.0001 *** a
FAQ	2.59 (3.12)	0.27 (0.48)	<0.0001 ***[a]
IQCODE	3.44 (0.63)	3.13 (0.23)	<0.0003***[a]

BDI= Beck Depression Inventory; BAI= Beck Anxiety Inventory; FAQ = Functional Activities Questionnaire; IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. (a) t test for independent samples (b) Chi-square. * p <0.01, ** p <0.001, *** p <0.0001.

Table 1. Clinical and sociodemographic characteristics and comparison between clinical subgroups and the healthy control group

Cognitive assessment

Table 2 shows that, after the stratification of the clinical group, due to cognitive impairment, a difference was observed in relation to age between the subgroups NC-PD and D-PD, severity of the disease between the subgroups D-PD and MCI-PD, NC-PD and MCI-PD, as well as for the NC-PD and DPD subgroups. Regarding the severity of the disease, assessed using the H&Y scale, a difference was observed between the subgroups, mainly between the NC-PD and D-PD ($\chi 2 = 12.5645$, $p = <0.0001$). The post hoc analysis (Bonferroni test) revealed that the DPD group had significantly lower mean scores for the total ACE-III score and in all five domains when compared to the NC-PD, MCI-PD, and healthy control groups. The comparison between the MCI-PD and healthy control groups showed that the MCI-PD group had only significantly lower mean scores in the total ACE-III and memory domain. The comparison between D-PD and MCI-PD, D-PD and healthy controls, D-PD and NC-PD showed statistically significant differences in all measures (total score of ACE-III and its five cognitive domains).

As for the cognitive tests of the neuropsychological battery (MDS level II assessment), there was a statistically significant difference between the total clinical and control groups regarding mental control measures, ROCF (copy, immediate recall, delayed recall), RAVLT (learning, list A; list B; A after interference, delayed recall, and recognition), phonemic verbal fluency (F-A-S), digit span (reverse order), Corsi block test (forward and reverse order), trail test (time of execution, parts A and B).

N=210	Controls (n=60)	NC-PD (n=24)	MCI-PD (n=104)	D-PD (n=22)	*p* value
ACE-III (total score)	87.02 (7.70)	92.42 (4.92)	82.05 (9.83)	69.27 (12.74)	<0.0001***
Attention/Orientation	16.88 (1.52)	16.92 (1.53)	16.13 (1.82)	14.18 (2.20)	<0.0001***
Memory	20.37 (3.89)	22.50 (3.02)	18.21 (4.26)	14.00 (5.01)	<0.0001***
Verbal Fluency	9.93 (2.68)	11.42 (1.64)	9.37 (2.73)	6.64 (2.87)	<0.0001***
Language	25.13 (1.29)	25.92 (0.28)	24.63 (2.11)	22.59 (3.32)	<0.0001***
Visuospatial	14.70 (1.57)	15.67 (0.48)	13.70 (2.67)	11.86 (3.27)	<0.0001***
Mental Control	5.7±0.6	5.6±0.6	5.2±1.0	4.2±1.6	<0.0001***
ROCFT (copy)	30.6±6.5	34.7±2.0	26.6±8.7	20.6±10.8	<0.0001***
ROCFT (sec)	307.1±144.4	286.0±157.8	377.0±251.3	401.2±243.3	<0.0640
ROCFT (immediate memory)	16.5±8.4	22.4±6.9	12.8±6.6	8.9±5.3	<0.0001***
ROCFT (delay memory)	16.2±7.8	22.9±5.4	12.0±6.3	8.4±5.2	<0.0001***
RAVLT - Total A	42.3±8.2	46.5±6.5	34.7±8.5	28.6±10.9	0.0001***
RAVLT - B	5.3±2.2	5.4±1.7	4.3±1.6	3.1±1.3	0.0001***
RAVLT - A (after interference)	8.1±2.8	10.2±1.9	6.4±2.6	5.7±2.5	<0.0001***
RAVLT - delayed memory	7.9±2.7	9.8±2.2	6.6±2.8	5.4±2.7	0.0001***
RAVLT - recognition	13.8±1.3	14.2±1.3	11.9±2.6	11.4±2.3	<0.0001***
Verbal Fluency (F, A, S)	33.6±11.6	37.0±11.3	26.09±9.9	19.2±8.6	<0.0001***
Verbal Fluency (animals)	15.5±4.3	18.4±4.9	14.8±4.9	10.7±4.3	<0.0001***
Digit Span (forward)	5.3±1.0	5.5±0.6	5.0±0.9	4.4±0.8	0.0001**
Digit Span (backward)	3.9±1.0	4.4±1.0	3.5±0.7	3.1±0.8	<0.0001***
Corsi Blocks (forward)	5.1±0.9	5.5±0.9	4.7±0.9	3.9±1.1	<0.0001***
Corsi Blocks (backward)	4.3±0.8	5.1±0.9	3.9±0.9	3.2±0.7	<0.0001***
TMT-A (sec)	67.4±31.1	56.3±26.3	88.3±61.7	111.4±64.4	<0.0004**
TMT-B (sec)	197.9±111.8	131.5±65.3	233.5±115.5	250.9±84.0	<0.0001***
TMT (B – A)	132.3±98.8	75.2±50.5	145.8±96.5	129.7±84.6	0.0106*

ACE-III = Addenbrooke Cognitive Examination, third version. ROCFT = Rey-Osterrieth Complex Figure Test. RAVLT = Rey-RAVLT Auditory-verbal Learning Test. VF = Verbal Fluency. TMT = Trail Making Test. One-way analysis of variance / ANOVA, with post hoc Bonferroni.

* p <0.01, ** p <0.001, *** p <0.0001.

Table 2. ACE-III scores and neuropsychological tests and comparison between the four subgroups.

Correlation between ACE-III, demographic, clinical data, and neuropsychological tests

Age was inversely associated with the total ACE-III scores and all of its cognitive domains, that is, score performance decreased when age increased; however, only the

domains verbal fluency, language, and visual-spatial showed significant correlation. On the other hand, the performance of cognitive scores was positively associated with years of formal education in all ACE-III scores. The higher the level of education, the better the performance on cognitive score (Table 3).

	Age (years)		Schooling (years)	
	r	r^2	r	r^2
ACE-III (total)	-0.1296	0.0167	0.4373***	0.0191
Attention/Orientation	-0.0336	0.0011	0.2685***	0.0720
Memory	-0.0339	0.0011	0.4257***	0.1812
Verbal Fluency	-0.1373*	0.0188	0.3368***	0.1134
Language	-0.1428*	0.0203	0.2693***	0.0725
Visuospatial	-0.1970**	0.0388	0.2925***	0.0855

* $p < 0.05$. ** $p < 0.01$, $p < 0.001$. Pearson's correlation (r). Determination coefficient (r^2).

Correlation coefficient: (= 1) perfect, (> 0.75) strong, (> 0.5) medium, (<0.5) weak, (= 0) nonexistent.

Table 3. Correlation coefficients and determination of scores by age and education (total ACE-III and its domains)

ACE-III: discriminant ability between subgroups/Diagnostic accuracy/ Diagnostic interpretation

Table 4 reveals the cut-off scores, sensitivity, and specificity of ACE-III, through analyses of the ROC curve. The ideal cut-off point for ACE-III to discriminate healthy controls was 85/100 (sensitivity=58.65%, specificity=60%). The AUC for ACE-III was 0.6400. To discriminate between healthy controls and DPD subgroup, the ideal cut-off point for ACE-III observed was 81/100 (sensitivity=77.27%, specificity=78.33%). The AUC for ACE-III was 0.8848.

ACE-III	MCI-PD	
Cut-off scores	**Sensivity**	**Specificity**
83	50.96%	71.67%
84	54.81%	66.67%
85	**58.65%**	**60.00%**
86	60.58%	55.00%
87	61.54%	51.67%
	D-PD	
78	72.73%	85.00%
79	72.73%	81.67%
80	77.27%	78.33%
81	**81.82%**	**75.00%**
82	81.82%	71.67%

Values: Bold data represents the optimal cut-off score (based on sensivity and specificity).

Table 4. Cut-off, sensitivity and specificity notes to identify MCI-PD and D-PD, using the total ACE-III score

When ROC analysis was performed by different levels of education years, the optimal ACE-III cut-off to discriminate D-PD from healthy controls, with 10-12 years of education, was 78 points, 100% sensitivity and 100% specificity, AUC = 1 (95% CI [1;1]); followed by >= 13 years (83 points, 75.00%: sensitivity and 100%: specificity, AUC = 0.9167 (95% CI [0.73; 1]) and 4-9 years (78, points, 81.82%: sensitivity and 62.50%: specificity, AUC = 0.8504 (95% CI [0.69; 1]). The optimal ACE-III cut-off to discriminate MCI-PD from healthy controls, with >=13 years, was 91 points (73.08% sensitivity and 77.78% specificity, AUC = 0.8312 (95% CI [0.67; 0.98]), followed by 10-12 years with 85 points (57% sensitivity and 74.07% specificity, AUC = 0.7089 (95% CI [0.60; 0.83]) and 4-9 years with 81 points (60% sensitivity and 50% specificity, AUC = 0.6110 (95% CI [0.46; 0.75]) (see Supplementary Tables 1-3).

DISCUSSION

The need for brief instruments, with good psychometric properties and accuracy to detect mild cognitive changes and dementia in DP is important in clinical practice. The frequency of MCI-PD and D-PD can be of 30% depending on age, disease duration, and comorbidities[29].

The third version (ACE-III) was only applied in the PD population by Lucza et al.[29], who aimed to compare the sensitivity and specificity of the different versions of ACE available in Hungary (ACE-I, ACE-III and Mini-ACE), to detect major and minor neurocognitive disorders, according to the DSM-5 criteria. ACE-III had the best diagnostic accuracy at all levels of education (cut-off points: 70.5, 77.5 and 78.5 points for individuals with educational level 0-8, 9-12 and > 12 years, respectively). Therefore, this study demonstrated that ACE-

III and its abbreviated version, M-ACE, had the best diagnostic accuracy to detect MCI-PD and D-PD.

The current study showed that ACE-III is a brief cognition assessment tool and is able to differentiate individuals with MCI-PD and D-PD from healthy controls, with cut-off scores of 85/100 and 81/100, to detect MCI-PD and D-PD, respectively.

Most studies used cognitive or brief screening batteries, such as MMSE, MoCA and MADRS, as a comparison method, with few studies including comprehensive neuropsychological batteries. The current study showed correlation of ACE-III domains with standardized neuropsychological tests for this population.

This study cut-off scores were lower than in studies with ACE[42] and ACE-R[43]. In this study, the instrument was used to distinguish the cognitive subtypes in PD (CN-PD, CCL-PD, D-PD=69), with a cut-off score of 88.5 being identified as capable of differentiating CN-PD from MCI-PD (with 0.68 sensitivity and 0.91 specificity) and 82.5 points (with 0.70 sensitivity and 0.73 specificity) to differentiate MCI-PD from D-PD, having an AUC of 0.78 (95% CI 0.63-0.93) [43]. This result was similar to the previous study by Biundo et al., (2013)[44] with a lower cut-off score of 80 points, but higher than the studies with the ACE-R in Brazil [45,46].

Thus, the studies were different from the current one in what regards education. The current one also has the highest average. The age and years of disease progression were similar, with minimal difference. Education influenced the total ACE-III score, regardless of the stratification of the clinical sample.

When analyzed by educational level, the results showed greater sensitivity and specificity to differentiate healthy controls from patients with D-PD. This is probably related to the fact that among patients with low education, low cognitive scores may signal disease and poor schooling simultaneously, and patients with low education may perform poorly without having cognitive impairment.

These aspects should be considered when interpreting the cut-off scores, to improve the accuracy of cognitive performance and the cognitive diagnosis.

Therefore, this study suggests that ACE-III was able to detect the presence of cognitive impairment in patients with PD. Thus, this battery can be used as a quick and efficient tool in the assessment of cognitive deficits associated with PD, that is, it can be widely useful in clinical practice, even more so in hospital contexts, where the application of sensitive and brief instruments is required. A combination with neuropsychological instruments is required, especially in those individuals with higher level of education and/or milder/initial deficits, to avoid false negatives. Although ACE-III application time is longer than that of other batteries, such as the MoCA, it has better accuracy in this population for the diagnosis of cognitive impairment.

The current study had the following strengths: (1) the analysis of the clinical utility and psychometric properties of ACE-III among PD subgroups. (2) the use of comprehensive

and standardized neuropsychological instruments for this clinical condition as a method of comparison. (3) Matching the clinical group with the healthy control group in terms of age, education, and sex contributed to the results of this study, strengthening the statistical analyses.

There are some limitations in the present study: (1) the participants were recruited from a rehabilitation hospital; therefore, the result is subject to reference bias and may not be applicable to community populations. (2) non-motor aspects (fatigue, insomnia, for example) may have influenced cognitive and functional results, as scales were not used for this purpose; however, when any interference of these aspects was observed, the evaluation was interrupted and continued later. The sample size of the subgroups was relatively small, mainly in relation to the CN-PD and D-PD. This aspect may have reduced the magnitude of the difference between the clinical group and the control group. Future studies with larger samples are required to add to these results.

ACKNOWLEDGEMENTS

The authors would like to thank Eneida Mioshi, for having given permission to use the instrument, and all the participants involved in this study.

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