Motor and functional changes in different stages of Alzheimer's disease

Alterações motoras e funcionais em diferentes estágios da doença de Alzheimer

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Abstract

Background: Alzheimer's disease (AD) is the most prevalent dementia, being associated with cognitive, behavioral, and functional alterations. However, clarifying the influence of the disease worsening in the decline of these functions is of major relevance. **Objective:** Compare specific cognitive functions, motor functions and activities of daily living (ADL) of AD patients in different stages of the disease. **Methods:** Cognitive and motor functions, as well as ADL of 74 AD patients (35 patients CDR1; 20 patients CDR2; 19 patients CDR3) were evaluated. **Results:** Motor function and independency in the ADL have presented a non-linear decline. While motor function shows a greater decline from the mild to the moderate phase, ADL present a greater decline in the severe stage of the disease. **Discussion:** Motor function decline is more evident in both moderate and severe stages of AD, associated with losses in physical capacity and increases in risk of falls. The patients' loss of independency to perform instrumental ADL occurs in a non-linear pattern and it is much greater than both physical and cognitive declines when these parameters are objectively evaluated in the three phases of the disease.

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Keywords: Functional capacity, dementia, mobility, cognition.

Resumo

Contexto: A doença de Alzheimer (DA) é a demência de maior prevalência e está associada a alterações cognitivas, comportamentais e funcionais. Entretanto, faz-se necessário esclarecer a influência do agravamento da doença no declínio dessas funções. **Objetivo:** Comparar funções cognitivas específicas, funções motoras e atividades de vida diária (AVD) de pacientes com DA em diferentes estágios da doença. **Métodos:** Foram avaliadas as funções cognitivas, as funções motoras e as AVD de 74 pacientes com doença de Alzheimer (35 pacientes CDR1; 20 pacientes CDR2; 19 pacientes CDR3). **Resultados:** A função motora e a independência das AVD apresentam declínio não linear. Enquanto a função motora apresenta maior declínio na fase leve para moderada, as AVD básicas sofrem maior declínio na fase grave da doença. **Conclusão:** O declínio motor é mais importante nas fases moderada e grave, associado a valores de perda de capacidade física e risco de quedas. Verifica-se que a perda de independência para realização das AVD instrumentais dos pacientes é muito maior do que o declínio físico e cognitivo avaliado objetivamente nas três fases da doença.

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Palavras-chave: Capacidade funcional, demência, mobilidade, cognição.

Introduction

The prevalence of dementia increases as longevity rises, reaching 20% in Latin America[1] and specifically 38.9% in Brazilian elderly with more than 85 years of age[2]. Currently, the global cost involved in the treatment of dementia represents 315 million dollars per year, with the annual cost reaching US$ 17,964.00 per patient. The progressive loss of autonomy, as well as the progressive dependence and necessity of specific care contribute for the high risk of institutionalization[3]. For these reasons, cognitive decline and mental diseases in ageing persons have become a major public health problem[3].

Functional capacity may be defined as the ability to perform basic (BADL) and instrumental (IADL)[4] activities of daily living. The IADL (most complex activities) require a better cognitive status (they are associated with self-management tasks), whereas BADL are related to self-care. Both motor function (strength, flexibility, aerobic capacity, and balance), and cognitive function (executive function, attention, and memory) influence the autonomy to perform activities of daily living (ADL). The ADL are progressively impaired in the AD patient, which increases the demand for care of family members and/or caregivers. AD patients only present impairments in BADL in the severe stage of the disease, although IADL may be impaired at all phases[5].

In the earlier stages of the disease, we often find loss of episodic memory and difficulty in the acquisition of new tasks. These damages gradually evolve to other cognitive impairments, such as judgment capacity, calculus, abstract reasoning, and visuo-spatial abilities. Fluent aphasia may occur in the intermediate phases, presenting as difficulty in naming objects or choosing the right words to express an idea, as well as apraxia. In the terminal stages of the disease, some remarkable changes may be observed, such as alterations in sleep-wake cycle, behavioral changes (irritability and aggressiveness), psychotic symptoms, and inability to walk, speak and perform self-care[5]. The progressive deficits in explicit memory (since explicit memory is needed for the functioning of the procedural memory) theoretically explains the functional decline pattern from IADL to BADL[6]. The global cognitive impairment is related to the functional decline, but the executive dysfunction may explain only 17% of the variations in the IADL and 9% of the variations in the BADL in AD patients[6].

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Despite the linear cognitive decline in AD, loss of autonomy in the ADL does not follow the same pattern, becoming necessary to understand the features which influence the alterations caused by the worsening of the disease.

In addition to cognitive changes and impairments in ADL, motor abnormalities may also be observed in AD patients. Gait disturbances (diminished gait velocity, reduced step length, and reduced step width), decreased limb strength[7], and changes in postural control may be present in the initial phases of dementia or even in the pre-clinical stage of AD. Elderly with mild cognitive impairment already present reduced balance and coordination and declined levels of physical activity, leading to increased risk of lesions, falls, and fractures[8]. Accordingly, 60% of elderly patients with cognitive decline suffer falls, twice more than those without impairment[8]. All of these changes are associated with the loss of independency and quality of life.

The aim of the present study was to compare specific cognitive functions (*memory, attention, executive function, and speed processing*), motor functions (*dynamic balance, gait, physical fitness, and flexibility*), and ADL of AD patients in different stages of the disease. Although there might be a constant decline of all evaluated functions, we expect that the impact of these detrimental changes in ADL will not occur in a linear manner.

Methods

Subjects

The sample of this cross-sectional study was composed by patients with ages ranging from 60 to 85 years, diagnosed with AD according to the *National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association* (NINCDS-ADRDA) in the three stages of the disease (mild, moderate, severe), based on the results obtained after the application of the Clinical Dementia Rating Scale (CDR). All patients have been treated in the Center for Alzheimer's disease and were taken acetylcholinesterase inhibitors (Rivastigmine and Donepezil) (Table 1).

Furthermore, the recruitment of healthy elderly subjects has been conducted through a convenience sample in order to obtain normative data to their corresponding ages. Subjects with sequel of cerebrovascular accident, comorbidities with other neurodegenerative diseases, mood disorders, use of psychoactive medication, patients unable to perform the physical tests and illiterate were excluded from the study, since these clinical conditions may be confounding factors in both motor and cognitive deficits of AD. This study was approved by the Ethics Committee of the Institute of Psychiatry of the Federal University of Rio de Janeiro, and all participants signed informed consent forms before the procedures.

Instruments

Physical evaluations, cognitive tests, and ADL assessments have been applied in the subjects of the study. All the assessments have been done on the same day and have lasted for approximately two hours, with the cognitive tests being assessed before any other evaluation. Then the functional tests and ADL assessments have been performed. The specifications of the evaluations are described below:

1. Cognitive assessment

(a) Trails A[9] (ability to maintain mental engagement, visual tracking, motor skills, and operational memory), (b) digit span[10] (verbal attention and operational memory), (c) Rey's test of auditory-verbal learning[11] (recent memory, learning, susceptibility to interference, retention after other activities, and recognition memory), (d) CAMCOG[12] (fixation memory, evocation and recognizing, language, praxis, executive function, besides the global cognitive evaluation by the Mini-Mental State Examination – MMSE), (e) clock test[12] (executive function, visual, spatial, and constructive abilities, (f) verbal fluency test[12] (executive function, semantic memory, and language), and (g) MMSE[12].

2. Motor function assessment

(a) POMA-BR[13] (balance and gait), (b) Berg[14] (functional evaluation of balance performance), (c) functional reach test[14] (ability in controlling the dislocation of the center of gravity on a fixed base of support), (d) timed up and go test[15] – TUG (basic functional mobility), (e) modified timed up and go test – mTUG (balance and verbal fluency), and (f) sit and stand test[15] (dexterity in the performance of sit and stand test, and lower limb strength).

3. ADL assessment

(a) Lawton[16] (patient's ability to perform IADL), (b) Pfeffer's questionnaire[17] (functionality), and (c) Katz Index[18] (patient's ability to perform BADL).

Table 1. Descriptive analysis (average and standard deviation) of AD patients according to the severity of the disease (CDR1, CDR2, CDR3) and healthy elderly

Variables	CDR 1 (n = 35)	CDR 2 (n = 20)	CDR 3 (n = 19)	F	p value
Age (years)	76 (7)	74 (7)	77 (11)	0,72	0,49
Education (years)	8 (5)	6 (3)	5 (3)	6,39	0,04**
Duration of disease (years)	4 (2)	4 (3)	4 (3)	36,00	0,27
Gênero feminino n (%)[a]	26 (74%)	18 (90%)	13 (70%)	1,27	0,52
Marital status n (%)[a]					
Single	6 (18%)	1 (10%)	0 (0%)		
Married	21 (59%)	8 (40%)	9 (47%)	4,00	0,05
Widowed	8 (23%)	10 (50%)	10 (53%)		
Comorbidities	1 (1)	1 (1)	2 (2)	15,76	0,10
Medication	2 (2)	2 (2)	2 (1)	15,21	0,50
Falls	0 (1)	1 (1)	0 (1)	3,39	0,75
MMSE (points)	20 (4)	14 (4)	6 (5)	47,40	0,00*

* Significant difference among the 3 groups.
** Significant difference from group 1 regarding to group 3.
p Value among CDR1, CDR2, and CDR3.
[a] Non-parametric tests: values are presented as median and interquartile deviation, and p value is referent to X^2.
MMSE: Mini-Mental State Examination.

These tests demonstrated high validity and interrater reliability[9-18].

Statistical analysis

For the comparison among the three groups (CDR1-mild, CDR2--moderate, and CDR3-severe) an ANOVA One-way has been applied to the parametric variables and the Kruskall-Wallis test has been applied to the non-parametric data. The software SPSS® (version 15.0) was used in the statistical analysis. The significance level accepted in this study was $p \leq 0.05$. To evaluate the effect size (ES) of all groups (CDR1, CDR2 e CDR3) the Cohen's ES has been performed by the following formula: ES = M1-M2/Pooled SD; where M1 = average of a reference group of healthy elderly (age = 63 ± 3 years; education = 11 ± 5 years; MMSE = 28 ± 3 points). According to Cohen, the ES has been classified as trivial (≤ 0.5), moderate (0.5-0.8), or strong (≥ 0.8).

Results

Descriptive analysis of the sample has shown that the three groups (CDR1, CDR2 and CDR3) did not present significant differences regarding to age, duration of disease, sex, and marital status. Education has shown significant difference from CDR1 group in relation to CDR3 group (CDR1 > CDR3). As expected, MMSE results presented significant differences among the groups, where CDR1 > CDR2 > CDR3.

CDR1 group has presented better performance than CDR2 group in all cognitive tests. A significant difference in performance between CDR2 and CDR3 has also been observed (CDR1 > CDR2 > CDR3). Results of direct order digit span, reverse order digit span, and total score digit span have presented significant differences in verbal attention, speed processing, operational memory, and executive function in CDR1 group when compared to both CDR2 and CDR3 groups, showing that CDR1 patients have better performance than the other two groups. There were no significant differences in Trails A test. These data are represented in table 2.

The results of physical capacity assessments pointed out to an important performance decrease in the CDR2 group (Table 3). Significant differences were found in Berg Scale, modified time up and go test, sit-and-stand test, total POMA, POMA gait and POMA (balance and functional reach) when CDR1 group was compared to both CDR2 and CDR3 groups.

With the worsening of symptoms, autonomy in BADL and IADL has been significantly inferior. Katz scale has showed significant difference in independence levels in both CDR1 and CDR2 groups compared to CDR3, because of the better performance of these first two groups. Table 3 shows the results of ADL.

There has been a large effect size (ES > 0.8) in the decline of basic and instrumental activities of daily living at all stages of AD. This behavior was increasing and linear according to the worsening of the disease (CDR1 < CDR2 < CDR3). However, the ES was much more expressive in the evaluation of independency in IADL of AD patients, showing ES values greater than 7.0 to these activities. ES values of cognitive function, motor function and ADL are represented in the figures 1, 2, and 3.

Table 2. Comparison of cognitive function among the three groups of AD patients (CDR1, CDR2, and CDR3

Variables	CDR1 N = 35	CDR2 N = 20	CDR3 N = 19	F	p value
CAMCOG (points)	72 (13)	41 (12)	11 (9)	35.31	0.000*
Clock test (points)[a]	2 (1)	1 (1)	0	40.33	0.000*
Words list (A1+A2+A3+A4+A5) (points)[a]	22 (8)	13 (8)	4 (5)	33.31	0.000*
Direct order span (points)	5 (2)	3 (2)	2 (2)	18.34	0.000**
Reverse order span (points)[a]	3 (2)	2 (1)	1(1)	34.20	0.000**
Total score digit span (points)	8 (3)	4 (2)	3 (2)	35	0.000**
Trails A (sec)[a]	152 (93)	206 (81)	-	2.49	0.123

* Significant difference among the 3 groups.
** Significant difference from group 1 compared to groups 2 and 3.
[a] Non-parametric test: values are presented as median and interquartile deviation, and p value is referent to X^2.

Table 3. Comparison of physical and functional variables among the three different AD groups (CDR1, CDR2, and CDR3)

Variables	CDR1 (n = 35)	CDR2 (n = 20)	CDR3 (n = 19)	F	p value
POMA balance (points)[a]	36 (2)	30 (11)	29 (9)	16.60	0.000***
POMA gait (points)[a]	17 (2)	15 (6)	14 (5)	7.14	0.028***
POMA sum (points)[a]	53 (4)	44 (16)	44 (14)	17.52	0.000***
Berg (points)[a]	49 (5)	42 (10)	35 (13)	26.24	0.000***
Pfeffer (points)[a]	11 (6)	20 (8)	27 (4)	41.67	0.000*
Katz (points)[a]	6 (4)	5 (1)	2 (2)	36.22	0.000****
Lawton ABVD (points)[a]	3 (2)	6 (4)	11 (3)	39.44	0.000*
Lawton AIVD (points)[a]	26 (12)	39 (13)	56 (6)	39.74	0.000*
Lawton soma (points)[a]	28 (12)	45 (16)	68 (8)	43.78	0.000*
TUG (sec)	8 (2)	13 (6)	18 (10)	15.46	0.000*
mTUG (sec)	12 (3)	21 (7)	23 (10)	17.11	0.000***
Sit-and-stand (repetitions)	9 (2)	7 (3)	5 (3)	15.48	0.000***
Functional reach (cm)	18 (6)	12 (8)	6 (6)	21.60	0.000***

* Significant difference among the 3 groups.
*** Significant difference from group 1 compared to groups 2 and 3.
**** Significant difference from groups 1 and 2 compared to group 3.
[a] Non-parametric test: values are presented as median and interquartile deviation, and p value is referent to X^2.

TUG: Timed Up and Go.

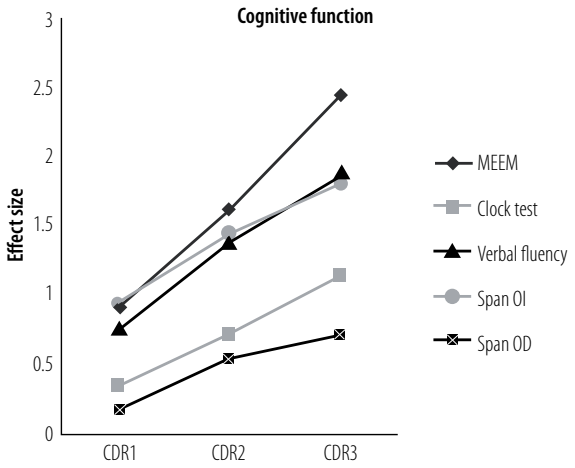

Figure 1. Effect size (ES) in cognitive performance of CDR1, CDR2, and CDR3 patients compared to healthy elderly at the same age. The larger the ES, the greater the impairment in cognitive function of the patients.

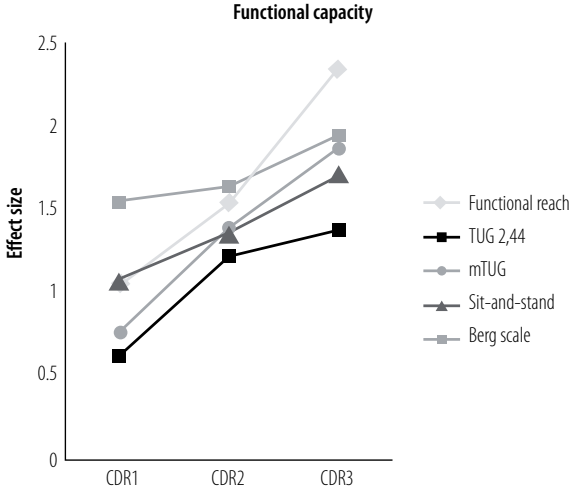

Figure 2. Effect size in motor performance in CDR1, CDR2, and CDR3 patients compared to healthy elderly at the same age. The larger the ES, the greater the impairment in the motor function of the patients.

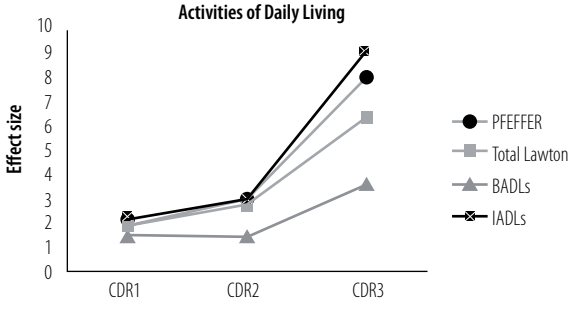

Figure 3. Effect size in independency in ADL (basic and instrumental) of CDR1, CDR2, and CDR3 patients compared to healthy elderly at the same age. The larger the ES, the greater the independency in the ADL of the patients.

Discussion

This study sought to investigate the alterations in motor and cognitive function, and ADL in AD patients in the three stages of the disease. The most relevant finding of the present investigation was the fact that the greatest motor decline occurred in the moderate and severe phases compared to the mild stage of AD. Despite the fact that decline in motor, cognitive, and functional capacities may be observed since the beginning of AD, this decline does not occur uniformly in the different stages of the disease. The loss of independence of the patients to manage ADL is not consistent with the physical and cognitive decline observed by the physical and neuropsychological tests.

As expected, cognitive function has showed a continuous decline with the evolution of the disease. However, the same behavior could not be seen in motor function. In the present study, the greater impairment has been observed between the mild and moderate phases in this domain. CDR1 patients have presented motor function similar to that expected to healthy elderly. This finding is in accordance with the literature, once studies have been showing that the risk of fall is similar in AD patients and healthy elderly in the mild stage of the disease. However, motor processes regulated by complex cortical mechanisms (such as sitting and rising from a chair) may be affected in both mild and moderate AD stages, predisposing patients to the risk of falls[19]. In the present investigation, moderate and severe AD patients have been at risk for functional loss and falls, much greater than expected to healthy elderly, in the Senior Fitness Test, and in Berg and POMA scales. Changes in motor function in AD may occur because of use of psychotropic drugs, extrapyramidal signs, myoclonus, and frontal gait, raising the risk of falls, institutionalization, and death in this population[20].

In the present study, ADL impairment has occurred in a different manner when compared to cognitive decline and motor function. Despite IADL have declined since the initial phases, BADL have declined only in the severe stage of the disease. This finding is in accordance with the literature, since studies have been demonstrating that patients present decline in IADL performance in the mild stage of AD, and impairment in BADL only becomes posteriorly[21]. In the initial stage of AD, patients were able to perform BADL[22], presenting impaired capacity in such activities in more severe stages of the disease[23] This decline in BADL is not evident until moderate and severe stages[7]. Moreover, deficits in BADL may develop for more than one decade[24].

In the severe phase, patients may completely lose the ability to perform IADL, although functional decline may be observed since the initial stages of AD[23]. Declines in IADL and BADL may overlap during moderate and severe stages of the disease[4] AD patients suffer a progressive loss in the abilities to live independently because of cognitive impairment and poor memory functioning[25]. While both BADL and IADL are affected in AD, IADL are the first ones to decline. Basically, functional impairment is the distinction point between AD and mild cognitive impairment[22].

A follow up study including 107 AD patients who have been evaluated at baseline, 6 months, and 12 months later showed that patients did not present deficits in BADL even in the presence of severe cognitive impairment, whereas IADL were affected in the initial phase of the disease[26]. Another study with a sample of 34 AD patients who were evaluated at baseline, 18 months, and 24 months later has found a strong relationship between cognition and IADL in the initial stages of AD. Such association becomes weaker as the disease progresses, increasing the association with psychiatric symptoms[27].

There seems to be a stronger relationship between IADL results and cognitive performance than between BADL and cognitive function[22]. As IADL require a more complex neuropsychological organization, such activities are much more vulnerable in the early stages of cognitive decline[4]. Theoretically, the progression of the deficit from explicit memory to procedure memory explains the earlier declines in IADL and, later, in BADL. The decline in IADL takes place when the episodic memory deficit becomes apparent, since this type of memory is of major importance in the performance of such activities.

The procedure memory keeps its normal until the later stages of AD, making the BADL preserved until the later stages of the disease[28].

On the other hand, a novel finding in this study was the large size effect observed between CDR2 and CDR3 for ADL (ES > 0,8). Although all functions are impaired in the physical and cognitive assessments in the three stages of the disease, the independence in IADL is not altered the same way. We have observed a greater decline in ADL than in motor and cognitive functions. This may be associated with the fact that the caregiver might underestimate or overestimate the patient's capacity in realizing ADL. Another possibility could be the lack of sensibility of the physical and neuropsychological tests to determine the real limitations of the patients for the necessities presented in daily living, in both basic and instrumental activities.

The findings of the present study are of major relevance, since they allow the identification of cognitive decline, motor impairment, and functional prejudice in each stage of AD, helping to develop strategies for prevention and treatment of disease.

Exercise may be used as a preventive strategy, since studies shown that its regular practice is of great importance in maintaining balance, strength, and cognition in AD patients[29,30]. Furthermore, exercise is associated with lower prevalence and incidence of dementia (32%), as well as cognitive decline[30]. Studies demonstrate that general exercise programs (endurance, mobility, and coordination) may slow down the deterioration in ADL performance, significantly increase global functional capacity, and raise the ability to perform ADL independently[29].

Some limitations must be considered in the present investigation. Because it is a cross-sectional study, one may not establish a cause-effect relationship among the disease staging and cognitive impairment, functional decline, and motor changes. In addition, the sample size may have influenced the results.

In summary, this study showed a linear decline in all global cognitive functions and increased motor decline occurring between mild and moderate stages of AD. Regarding ADL, a non-linear decline could be observed, being more evident in the moderate and severe phases of the disease. We found that the loss of independence in carrying out IADL of patients is much larger than the physical and cognitive decline as objectively assessed in moderate and severe stages of the disease.

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