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Correlations among cognitive and behavioural assessments in patients with dementia due to Alzheimer's disease

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ABSTRACT

Aims: Primarily, we sought to verify correlations among assessments for cognition, behaviour and functional independence in a sample of patients with dementia due to Alzheimer's disease (AD). Secondarily, impacts of education, *APOE* haplotypes, length of dementia, age and alcohol use over the neuropsychiatric assessment were estimated.
Methods: Patients with AD were assessed for demographic features, neuropsychiatric symptoms, cognitive test scores, functional impairment, caregiver burden and *APOE* haplotypes. Statistical comparisons were undertaken by way of Kruskal–Wallis test, linear regressions and Spearman correlations, significance at $\rho < 0.05$.
Results: A total of 217 patients were included. Mean schooling was 4.21 ± 3.7 years, with significant impacts over cognitive tests. Mean age at examination was 78 ± 6.19 years-old, significantly influencing instrumental functionality. The mean length of the dementia syndrome was 5.4 ± 2.9 years, significantly impacting cognitive decline and functionality. Apathy was the most common behavioural symptom, negatively correlated with anxiety and delusions, and positively correlated with lifetime alcohol load. Patients with previous smoking or drinking habits were more likely to continue smoking or drinking later in life. APOE4+ haplotypes led to earlier dementia onset and significantly lower caregiver burden in mild dementia stages.
Conclusions: Most correlations among test results were highly significant, confirming that cognition, behaviour and functionality are usually interrelated in all stages of AD. Caregiver burden was correlated with behaviour, but not with cognition, and was lower for patients with APOE4+ haplotypes in mild dementia stages. Education is a major impact factor for cognitive performance.

1. Introduction

Standardized scales are essential for diagnostic precision and for characterization of cognitive decline in dementia due to Alzheimer's disease. Brief instruments of cognitive and behavioural assessment are particularly useful for everyday evaluations. While the impact of schooling over such scales is highly regarded, it is still unclear how much other factors such as age, length of dementia, or regular alcohol use might bias test results.

Neuropsychiatric symptoms impact rates of cognitive decline and caregiver distress [1,2], but these effects are hardly measurable. Functionality usually follows cognitive test performance; yet again this is a seldom objectively reconnoitred matter. Knowledge of dementia severity and how much cognition correlates with behaviour and functional independence is crucial not only for management decisions but also for definition of proper endpoints and comparisons in research settings [3].

The primary aim of this study was to verify potential correlations among tests for cognitive and behavioural assessment, caregiver burden and functional independence in patients with dementia due to Alzheimer's disease (AD). Secondarily, impacts of education, *APOE* haplotypes, length of the dementia syndrome, age and alcohol use over the neuropsychiatric assessment were estimated.

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2. Methods

Consecutive outpatients with AD in several stages, diagnosed in accordance with National Institute on Aging – Alzheimer's Association criteria [4], were recruited from the Behavioural Neurology Section of *Hospital São Paulo*, Federal University of São Paulo – UNIFESP, from November 2010 to February 2013. After diagnostic confirmation, patients were assessed for: gender, age, schooling, marital status, estimated age of dementia onset, quantification of alcohol use or smoking, and scores on the Neuropsychiatric Inventory (NPI) [5], Mini-Mental State Examination (MMSE) [6], Severe Mini-Mental State Examination (SMMSE) [7], Clinical Dementia Rating (CDR) [8], CDR sum-of-boxes (CDR-SOB), a 15-item Clock Drawing Test (free drawing) (CDT) [9], the Index of Independence in activities of daily living (ADL) [10], Lawton's Scale for Instrumental activities of daily living (IADL) [11], and the Brazilian Version of the Zarit Caregiver Burden Interview (ZCBI) [12]. All evaluations were conducted on weekdays at morning time, by the same examiner (FFO).

For the validated CDT that was used in this study, patients were instructed to freely draw a clock that marked 11:10, setting hands and numbers on the face (repetition was allowed). Scoring comprised 15 items, each scored as zero or one: outer circle present and closed; acceptable circle diameter; intact sequence 1–12, with no omissions or intrusions; only Arabic numerals; correct sequential order of the numerals; paper is not rotated for number placement; proper symmetrical spacing; all numbers inside the circle; only two hands present; any mark to indicate the hour; any mark to indicate the minute; minute hand longer than hour hand; no pointless intrusions; both hands connected, or up to 2 mm space between them; centre of the clock drawn or inferred where hands meet.

The ADL reflects behavioural levels of six sociobiological functions: bathing, dressing, toileting, transfer, continence, and feeding. After caregivers were queried, each function was scored zero for dependency or one for independence, with an index total of zero to six. A trichotomous version (1 = unable; 2 = able with help; 3 = able without help) of IADL was employed, with scores for using the telephone, getting to places beyond walking distance, grocery shopping, meal preparation, housekeeping, doing handyman work, doing laundry, taking own medications, and handling finances; caregivers provided all information, with a total score of 9–27.

After blood samples were collected from all patients in tubes with EDTA 0.1%, genomic DNA was extracted for genotyping. *APOE* haplotypes were determined for all patients: SNPs rs7412 and rs429358 were assessed by way of Real-Time Polymerase Chain Reactions using TaqMan® SNP Genotyping Assays on the Applied Biosystems 7500 Fast Real-Time PCR System (Applied Biosystems®, USA), following the standard protocols of the manufacturer.

Statistical comparisons among groups according to *APOE* haplotypes or marital status were conducted by way of Kruskal–Wallis test. A multiple linear regression model was employed for correlations among each of the major test results and the following independent variables: schooling, estimated length of the dementia syndrome, and age at examination. Multiple linear regressions were calculated for each of the 10 items in the NPI and the following independent variables: schooling, estimated length of the dementia syndrome, estimated alcoholic drinking load throughout life, and scores on the MMSE. The Bonferroni test was employed for corrections of ρ-values in the multiple regressions. Simple linear regression models were employed for comparisons between independent test results. Spearman correlations were estimated for schooling, alcohol use, smoking, and for items from the NPI, ADL, IADL, ZCBI, and the MMSE. The threshold of significance was set at $\rho < 0.05$.

This study is part of the research project 1067/10 (CAAE 0540.0.174.000-10) approved by the Ethics Committee of *Hospital São Paulo*, Federal University of São Paulo – UNIFESP, on August 2010. All invited patients and their legal representatives agreed to participate on the research and signed the Informed Consent Form before the evaluation.

3. Results

3.1. Demographic and genetic results

A total of 217 patients were included; 147 were female (67.7%) and 70 were male (32.3%); 109 (50.23%) were married, while 6 (2.76%) were divorced, 19 (8.76%) were single, and 83 (38.25%) were widowers. Mean age at examination was 78 ± 6.19 years-old (range 60–95), mean estimated age of dementia onset was 73.19 ± 6.8 years-old (range 52–88), and mean estimated length of dementia was 5.4 ± 2.9 years (range 0.5–14.5).

Mean schooling was 4.21 ± 3.7 years (range 0–15). Overall mean alcohol use was 17.25 L per year (range 0–315), while 56 patients (25.8%) had history of alcohol use, and 11 (5.1%) were regularly drinking at survey time. Overall mean smoking was 48.75 packs per year (range 0–700), while 79 patients (36.4%) had smoking history, and 14 (6.5%) were regular smokers at survey time. Spearman correlations for schooling ($\rho < 0.0001$) were negative regarding alcohol use at any time ($r_s = -0.0216$) and current smoking ($r_s = -0.0146$), and positive for current alcohol use ($r_s = 0.0789$) and smoking at any time ($r_s = 0.0513$). Spearman correlations were also significant ($\rho < 0.0001$) between alcohol use at any time and smoking at any time ($r_s = 0.3849$), current alcohol use and smoking at any time ($r_s = 0.1434$), alcohol use at any time and current smoking ($r_s = 0.1488$), current alcohol use and current smoking ($r_s = 0.0225$), alcohol use at any time and currently ($r_s = 0.3550$), and smoking at any time and currently ($r_s = 0.3917$).

With regard to *APOE* haplotypes, there were 26 $\varepsilon4/\varepsilon4$, 81 $\varepsilon4/\varepsilon3$, 7 $\varepsilon4/\varepsilon2$, 93 $\varepsilon3/\varepsilon3$, and 10 $\varepsilon3/\varepsilon2$; in other words, 114 were APOE4+, and 103 were APOE4−. Earlier onset of dementia was correlated with APOE4+ in patients with CDR = 2.0 ($\rho = 0.019$) and with the $\varepsilon4/\varepsilon4$ haplotype in patients with CDR = 1.0 ($\rho < 0.007$). For patients with CDR = 1.0, scores on the ZCBI were lower for APOE4+ haplotypes ($\rho = 0.002$, Table 1).

A simple linear regression revealed that only 0.2% of the variability in NPI scores could be explained by the length of the dementia

Table 1
Statistical comparisons according to *APOE* haplotypes.

CDR[a] scores	*n*		Mean ± SD[b] for age of dementia onset (years-old)			Mean ± SD[b] for ZCBI[c] scores (0–56 points)		
	APOE4+	APOE4−	APOE4+	APOE4−	ρ-value	APOE4+	APOE4−	ρ-value
CDR[a] = 1.0	39	44	73.13 ± 6.4	73.07 ± 7.5	0.770	10.08 ± 8.3	16.34 ± 9.9	0.002
CDR[a] = 2.0	59	45	71.73 ± 6.5	75.00 ± 6.8	0.019	18.54 ± 10.4	18.91 ± 10.6	0.765
CDR[a] = 3.0	16	14	74.31 ± 6.5	72.89 ± 6.1	0.308	16.12 ± 13.2	20.14 ± 10.8	0.227

[a] CDR, clinical dementia rating.
[b] SD, standard deviation.
[c] ZCBI, Brazilian Version of the Zarit Caregiver Burden Interview.