

Cognitive performance in patients with Mild Cognitive Impairment and Alzheimer's disease with white matter hyperintensities

An exploratory analysis

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ABSTRACT. Background: White matter hyperintensities (WMH) are commonly associated with vascular dementia and poor executive functioning. Notwithstanding, recent findings have associated WMH with Alzheimer's disease as well as other cognitive functions, but there is no consensus. **Objective:** This study aimed to verify the relationship between WMH and cognitive performance in Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD) patients. The study also sought to identify cognitive and demographic/cultural factors that might explain variability of WMH. **Methods:** The sample was composed of 40 participants (18 MCI and 22 AD patients) aged ≥ 65 years. Spearman's correlation was performed among cognitive performance (memory, language, visuospatial ability, and executive function) and WMH evaluated by the Fazekas and ARWMC scales. Two stepwise linear regressions were carried out, one with cognitive and the other with demographic/cultural variables as predictors. **Results:** Only naming showed significant correlation with ARWMC. Fazekas score exhibited significant correlation with all cognitive domains evaluated. Fazekas score was better predicted by episodic visual memory and age. **Conclusion:** This study found that the most relevant cognitive profile in MCI and AD patients with WMH was related to episodic memory. And, without taking clinical aspects into consideration, age was the best predictor of WMH.

Key words: Alzheimer's disease, Mild Cognitive Impairment, white matter hyperintensities, cognition.

DESEMPENHO COGNITIVO EM PACIENTES COM COMPROMETIMENTO COGNITIVO LEVE E DOENÇA DE ALZHEIMER COM HIPER-INTENSIDADES DE SUBSTÂNCIA BRANCA: UMA ANÁLISE EXPLORATÓRIA

RESUMO. Introdução: Hiperintensidades de substância branca (HSB) são comumente associadas à demência vascular e ao mau funcionamento executivo. Contudo, descobertas recentes relacionam-no com a doença de Alzheimer, bem como com outros funcionamentos cognitivos, mas não há um consenso. **Objetivo:** Este estudo teve como objetivo verificar a relação entre HSB e desempenho cognitivo em pacientes com Comprometimento Cognitivo Leve (CCL) e doença de Alzheimer (DA). Assim como, identificar fatores cognitivos e demográficos / culturais que poderiam explicar a variabilidade da HSB. **Métodos:** A amostra foi composta por 40 participantes (18 CCL e 22 pacientes com DA) com ≥ 65 anos de idade. A correlação de Spearman foi realizada entre o desempenho cognitivo (memória, linguagem, capacidade visoespacial e função executiva) e HSB avaliada através das escalas Fazekas e ARWMC. Dois modelos de regressão linear stepwise foram realizados, um com variáveis cognitivas e outro com variáveis demográficas / culturais como preditores. **Resultados:** Somente nomeação apresentou correlação significativa com ARWMC. Fazekas apresentou correlação significativa com todos os domínios cognitivos avaliados. Fazekas foi melhor predito pela memória episódica visual e idade. **Conclusão:** Este estudo foi capaz de identificar que em pacientes com CCL e DA com HSB o perfil cognitivo mais relevante está relacionado à memória episódica. E, sem levar em consideração os aspectos clínicos, a idade foi o melhor preditor da HSB.

Palavras-chave: doença de Alzheimer, Comprometimento Cognitivo Leve, hiperintensidades de substância branca, cognição.

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INTRODUCTION

Alzheimer's disease (AD) is traditionally characterized by amyloid-beta extracellular amyloid-positive neuritic plaques and intracellular tau-positive neurofibrillary tangles. However, recent findings identify that white matter hyperintensities (WMH) could play an important role, proving even more strongly associated with preclinical AD than other AD biomarkers.¹ WMH are commonly associated with vascular neurodegenerative diseases, which are a consequence of vascular risk factors and lead to vascular cognitive impairment.² Cerebrovascular lesions are found in the majority of late-onset AD, with age representing an important factor related to cognitive impairment.³ Cerebrovascular lesions seem to be related to both elderly individuals with dementia and healthy subjects.^{4,5} Furthermore, the value of WMH findings in Alzheimer's disease (AD) is still controversial,⁶ because they can be found in AD patients and in vascular dementia patients. However, a recent study suggested that WMH are able to independently predict cognitive impairment in AD patients.⁷ WMH are mainly identified in frontal and parietal regions,^{4,8} and periventricular areas.⁵ The presence of WMC in the hippocampus can be supportive for memory decline, and atrophy of this region is now recognized as a good biomarker of the Alzheimer pathology.^{8,9}

WMH can be classified according to severity, extent and site of injury/change.^{4,10,11} Brain areas with greatest and most incipient lesions are detected by neuroimaging.⁴ The most used scales for the evaluation and classification of these vascular components are the Fazekas, used to describe the severity of periventricular and deep white-matter hyperintensities;⁶ and the Age Related White Matter Changes (ARWMC) which assesses white matter lesions and basal ganglia lesions.^{4,11} Some authors suggested that WMH are associated with sociodemographic factors such as age and previous medical history of hypertension, diabetes and cerebrovascular diseases that are widely associated as risk factors for cognitive impairment.^{4,5,11-13} Although WMH have been shown to be associated with age and vascular risk factors, the exact mechanisms explaining these association remain unclear.¹¹

Vascular cognitive impairment is a term used for the range of changes and impairments within a cognitive continuum associated with vascular pathologies,^{10,14-17} but that do not yet meet criteria for dementia. In contrast, Vascular Mild Cognitive Impairment (VaMCI) is a concept involving Mild Cognitive Impairment (MCI) that includes a clinical history of cerebrovascular disease, or diffuse WMH;¹⁸⁻²⁰ as well as impairment in at

least one cognitive domain, but without underlying functional impairment.^{10,18,21} Both VaMCI and MCI may have multiple cognitive components covered by the pathology, yet result in the same memory difficulties.²⁰ However, dementia and MCI due to AD present initial significant episodic memory impairment which progresses to impairments in other cognitive components.²² The first impairments in VaMCI are related to executive functioning, semantic memory, visuospatial skills, attention and perception.²² Nonetheless, the executive components of processing speed, switching, and inhibitory control could be more closely associated with the extension of the WMH.¹⁹ Many of the studies on WMH associated with cognitive functions investigated only one specific cognitive domain, or carried out comparison with vascular dementia.^{18,21,22}

Thus, it is known that sociocultural factors are strongly related with dementia and inherent cognitive impairment, with aging being the main risk factor for the development of dementia.²³ Brain atrophy also increases significantly with advancing age.¹² Thus, it is necessary to understand which structural, cognitive and sociocultural factors are related to the profile of MCI patients with greater vascular components. Therefore, there is still a lack of information allowing the establishment of this explanatory cognitive profile for patients with MCI and dementia due to AD with greater WMH. Thus, the aim of this study was to determine whether there is a relationship between the amount of vascular components (as expressed by degrees of WMH) and cognitive performance (episodic and visual memory, language, visuospatial ability and executive function) in amnesic MCI patients and patients with dementia due to AD. In an exploratory study, we estimated the strength of the association of different cognitive domains with WMH scores. We also sought to identify cognitive and demographic/cultural factors (sex, age, education, frequency of reading and writing habits) that might explain variability of vascular components.

METHODS

Participants. The initial sample consisted of 55 participants, 30 MCI and 25 mild AD patients. The patients were recruited from the Dementia Clinic of the Hospital das Clínicas de Porto Alegre (HCPA) and through media advertising (television, radio and internet). The diagnostic criteria used for amnesic MCI patients were those of Winblad et al. (2004).²⁴ For MCI diagnosis, patients had to have a performance of 1.5 SD below normative data on the Rey Auditory-Verbal Learning Test (delayed recall). Diagnosis of dementia due to AD

was based on the current diagnostic criteria for probable or possible Alzheimer’s disease of the National Institute of Neurologic and Communicative Diseases and Vascular Cerebral Accident and Alzheimer Disease Related Association (NINCDS-ADRDA) criteria.^{9,25} Only history of concomitant vascular disease was accepted for inclusion contributing to the possible clinical manifestations of AD.²⁶ All other concomitant pathologies were excluded. Patients with dementia due to AD had to be classified with mild severity as assessed by the Clinical Dementia Rating Scale (CDR)^{26,27} or with a scores on the Mini-Mental State Examination (MMSE) > 14,²⁸ or on the Activities of Daily Living Questionnaire (ADL-Q) < 66.²⁹

Participants with sensory disturbances (auditory and/or visual) without correction; current or prior history of substance abuse or dependence; neurological disorders (epilepsy, tumor, TBI) were excluded. Mild current depressive symptoms, as assessed by the Geriatric Depression Scale (GDS-15) ≤ 6,^{30,31} were not a basis for exclusion because this symptomatology may be present in MCI patients³² or mask common features at the onset of dementia such as apathy.³³

Preliminary analyses identified the influence of age as responsible for the differentiation of the amount of vascular components among MCI and dementia patients. Therefore, the analysis of this study only included patients over 65 years of age (number of excluded participants = 15). Thus, the final sample was composed of 40 elders, comprising 18 amnesic MCI and 22 patients with mild dementia due to AD.

Procedures and instruments. The study was approved by the Research Ethics Committee of the Pontifical Catholic University of Rio Grande do Sul (number 657.955). All participants provided written consent for participation, and a family member/caregiver also provided written consent for AD patients. All subjects were assessed individually in noise-free rooms. Assessments were carried out in up to three evaluation sessions that lasted approximately one to two hours each, under appropriate conditions in accordance with ethical guidelines for research with human participants. All interviewers were instructed to monitor patients with signs of fatigue and to interrupt the session when this appeared to be interfering with the participant’s performance.

Participants answered a sociocultural and health aspects questionnaire to identify inclusion and exclusion criteria. This semi-structured questionnaire encompasses questions about sex, age, education, frequency of reading and writing habits,³⁴ use of medications, description of onset and progression of forgetfulness symptoms, or functional impairment. It also assesses socioeconomic status according to the Brazilian Association of Companies and Research.³⁵ The other instruments used for evaluation were divided by domain and are presented in Table 1.

All participants underwent 1.5T MRI scans of the brain at the Radiology Department of HCPA. A qualified neurologist who was a specialist in the field of dementia evaluated all scans. For reliability, 30% of the scans were drawn for a blind reassessment and concordance was 100%.

Table 1. Instruments for cognitive evaluation.

Global Cognition	<ul style="list-style-type: none"> • Mini-Mental State Examination (MMSE): evaluates aspects of global cognition such as orientation, calculation, attention, memory and language.^{36,37,38}
Memory	<ul style="list-style-type: none"> • Rey Auditory-Verbal Learning Test (RAVLT): we use this instrument to measure long-term episodic verbal memory (RAVLT-A7).^{39,40} • Brief Neuropsychological Assessment Battery (NEUPSILIN): subtests of prospective memory and semantic memory.⁴¹ • Consortium to Establish a Registry for Alzheimer’s Disease (CERAD): subtest of praxis recall to estimate episodic visual memory.⁴²
Executive Function	<ul style="list-style-type: none"> • Wechsler Adult Intelligence Scale (WAIS-III): digit span subtest to evaluate working memory.^{43,44}
Language	<ul style="list-style-type: none"> • Montreal–Toulouse Language Assessment Battery (MTL): auditory comprehension and naming subtests.^{45,46} • Montreal Communication Evaluation Battery (MAC): unconstrained, phonological and semantic verbal fluency subtests.^{47,48}
Visuospatial ability	<ul style="list-style-type: none"> • Consortium to Establish a Registry for Alzheimer’s Disease (CERAD): constructional praxis subtest.⁴² • Brief Neuropsychological Assessment Battery (NEUPSILIN): subtest of clock drawing test to evaluate constructional praxis.⁴¹

Two different scales were used to evaluate WMH. The Fazekas scale measures the severity of periventricular and deep white-matter hyperintensities using a 0 to 3 point score.⁶ The Age Related White Matter Changes (ARWMC) scale assesses white matter lesions and basal ganglia lesions also using a 0 to 3 point score.⁴ On both scales, higher scores indicate more vascular component present in the brain.

Data analysis. Data were analyzed using the Statistical Package for Social Sciences (SPSS), version 23.0. Clinical, cognitive and demographic/cultural variables were compared between groups using the Mann-Whitney U test and Chi-square test. Spearman's correlation was performed among memory, executive function, language and visuospatial ability performance and Fazekas and ARWMC scores given the variables had a nonparametric distribution. We carried out two stepwise linear regressions. One with cognitive performance and Fazekas score, and the other with demographic/cultural aspects and Fazekas score. We only selected

the four cognitive variables with highest correlation with Fazekas score for the regression model because of the sample size.⁴⁹ Thus, episodic visual memory (praxis recall test), naming test, Mini-Mental State Examination and Clock Drawing Test were entered as independent variables in a stepwise linear regression model for Fazekas score. Age, education, sex and frequency of reading and writing habits were entered as independent variables in a stepwise linear regression model for ARWMC score. We did not carry out stepwise linear regression model for the ARWMC scale because only naming performance exhibited a significant correlation with the ARWMC scale. Results were considered significant at $p < 0.05$.

RESULTS

No significant differences for the demographic/cultural and clinical variables were observed between MCI and AD dementia patients. The groups showed significant differences on 4 cognitive tests (Table 2).

Table 2. Participant characteristics.

Variables	MCI (n=18) M (SD)	AD (n=22) M (SD)	p*
Age	72.94 (5.15)	77.27 (5.38)	0.307
Years of education	11.56 (5.56)	7.27 (6.44)	0.060
Frequency of reading and writing habits	11.28 (6.30)	6.23 (5.09)	0.060
Socioeconomic status	31.28 (10.53)	28.05 (7.60)	0.526
Fazekas score	2.11 (1.18)	2.86 (1.61)	0.097
ARWMC score	1.11 (0.58)	1.50 (1.10)	0.081
Mini-Mental State Examination	25.44 (3.97)	21.23 (4.45)	0.060
Episodic verbal memory (RAVLT- A7)	4.94 (2.98)	1.14 (1.91)	0.004
Episodic visual memory (CERAD – praxis recall)	5.28 (3.30)	2.36 (3.24)	0.067
Visuospatial ability (CERAD – constructional praxis)	9.56 (1.62)	8.41 (2.04)	0.112
Clock drawing test	2.39 (1.57)	1.59 (1.53)	0.033
Digit span	10.94 (2.84)	9.00 (2.31)	0.399
Auditory comprehension	17.50 (1.42)	15.91 (2.09)	0.032
Naming test	28.17 (1.88)	26.23 (2.71)	0.032
Unconstrained verbal fluency	38.17 (16.60)	25.55 (14.82)	0.060
Phonological verbal fluency	15.89 (7.39)	10.67 (4.25)	0.079
Semantic verbal fluency	17.00 (5.03)	12.00 (4.17)	0.040
Semantic memory	4.56 (0.86)	4.45 (0.67)	0.678
Prospective memory	1.28 (0.38)	0.83 (0.74)	0.002
Sex – Female – n (%)	14 (77.8)	16 (72.7)	1.000

$p \leq 0.05$ indicates significance. RAVLT: Rey Auditory Verbal Learning Test, CERAD: Consortium to Establish a Registry for Alzheimer's Disease.

Table 3 shows the correlations among cognitive performance, Fazekas and ARWMC scores. Tables 4 and 5 present the predictors that best explained the variability in the Fazekas score. The more intense the vascular components, the lower the performance in episodic visual memory (explaining 17% of this variability). The older the person, the greater the vascular component present (explaining 18% of this variability).

DISCUSSION

The main objective of the study was to evaluate the relationship between the vascular component measured by the Fazekas and ARWMC scales and the cognitive evaluation in MCI and AD patients. Secondly, an explanatory analysis was performed for both sociodemographic data and for cognitive data components in relation to the Fazekas scale. The results indicated a moderate,

Table 3. Spearman's correlation among memory, executive function, language and visuospatial ability performance and Fazekas and ARWMC scale scores.

Variables	Fazekas		ARWMC	
	rho	p	rho	p
Mini-Mental State Examination	-0.402	0.010	-0.105	0.518
Episodic verbal memory (RAVLT- A7)	-0.345	0.029	-0.235	0.145
Episodic visual memory (CERAD – praxis recall)	-0.445	0.004	-0.251	0.119
Visuospatial ability (CERAD - constructional praxis)	-0.286	0.073	-0.181	0.264
Clock drawing test	-0.366	0.020	-0.220	0.173
Digit span	-0.328	0.039	-0.190	0.240
Auditory comprehension	-0.346	0.029	-0.117	0.471
Naming test	-0.436	0.005	-0.352	0.026
Unconstrained verbal fluency	-0.338	0.033	-0.246	0.126
Phonological verbal fluency	-0.259	0.111	-0.165	0.315
Semantic verbal fluency	-0.320	0.047	-0.207	0.207
Semantic memory	-0.060	0.713	0.058	0.723
Prospective memory	-0.314	0.052	-0.069	0.678

p≤0.05 indicates significance. RAVLT: Rey Auditory Verbal Learning Test, CERAD: Consortium to Establish a Registry for Alzheimer's Disease.

Table 4. Stepwise linear regression of cognition and the Fazekas scale

Dependent variables	Predictors	B	SE	β	T	p	ΔR ²	F Change	Sig F Change
Fazekas	Model 1 Episodic visual memory	-0.174	0.061	-0.420	-2.849	0.007	0.176	8.118	0.007

p≤0.05 indicates significance.

Table 5. Stepwise linear regression of sociodemographic/cultural variables and the Fazekas scale

Dependent variables	Predictors	B	SE	β	T	p	ΔR ²	F Change	Sig F Change
Fazekas	Model 1 Age	0.112	0.038	0.430	2.940	0.006	0.185	8.643	0.006

p≤0.05 significant.

negative association between the Fazekas scale and the cognitive components of executive functions, episodic memory (verbal and visual) and language. The ARWMC only showed a moderate, negative association with naming performance.

The correlation analysis indicated that the Fazekas scale was associated with more cognitive factors than the ARWMC scale. The ARWMC scale showed only a moderate association with naming. In contrast with the Fazekas scale, besides periventricular and deep white matter lesions, the ARWMC scale also scores basal ganglia lesions. Although brain cortical areas are traditionally related to cognitive function including language,⁵⁰ the basal ganglia are more related to language functioning than to other cognitive functions,⁵¹ which could explain the association with the naming test in our sample. On the other hand, Fazekas score correlated with the executive components of organization, visuospatial planning, verbal cognitive flexibility, in addition to unconstrained and semantic verbal fluency, auditory comprehension and naming, and episodic memory (verbal and visuospatial).

The regression analysis for the cognitive components showed that only visual episodic memory significantly explained 17% of the Fazekas variance (i.e., the more vascular component present the lower the performance in episodic visual memory). Episodic memory deficit is commonly observed in amnesic MCI patients who subsequently progress to a diagnosis of AD dementia.⁵² Memory impairment is frequently the primary cognitive deficit in patients with dementia due to AD.⁹ By contrast, patients with vascular dementia showed more visuospatial difficulties than patients with probable AD.²² Previous studies have shown a diversified cognitive profile in patients with VaMCI depending on the characteristics of the sample compared. These studies reported impairment in executive functioning in VaMCI patients compared to normal controls¹⁹ and in attention/executive, memory and visuospatial functioning compared against individuals with small-vessel disease but without cognitive impairment,⁵³ and decreased impairment in episodic memory (verbal and visual) and executive functioning relative to MCI patients.⁵⁴

Regarding the sociodemographic components analyzed in the present study, age explained 18% of the variance found by the Fazekas scale. Some studies have suggested that age is strongly related to WMH.^{12,55} Together with age, WMH are risk factors for the development of neurodegenerative diseases such as AD.^{23,55} However, the explanatory model shows that age has

a small percentage of explanation. This was expected because clinical components such as hypertension, diabetes, previous stroke, among others, probably better explain the increase in white matter damage since they are risk factors for greater damage and risk of cerebrovascular diseases.^{4,11,13} Additionally, studies have shown that small-vessel cerebrovascular disease potentially contributes to the pathogenesis of AD,⁵⁶ while WMH contribute to brain atrophy patterns in regions related to Alzheimer's disease dementia⁵⁷ and can be more strongly associated with preclinical AD than other AD biomarkers.¹

Limitations of the present study should be considered. The small sample size and the use of the clinical diagnosis for the classification of amnesic MCI and dementia due to AD patients are probably important. We used the Fazekas and ARWMC scales to estimate number, location and intensity of WMH – not volume of WMH – which are less affected by brain volume measurements (and cerebral atrophy). However, the cortical thickness estimation for atrophy would control an important confounder for volume of WMH. Furthermore, studies with the inclusion of AD biomarkers would better classify patients into more specific clinical groups.

Surprisingly, the study was able to identify, even for patients with profiles of WMH, that the most relevant cognitive profile was related to episodic memory. This finding supports verbal and visual episodic memory as the main cognitive components to be evaluated in MCI and dementia due to AD patients. Further studies that explore specific cognitive components to detect vascular components in dementia would aid in interventions and orientations.

Author contribution. Maila Rossato Holz supervised the data collection, was responsible for carrying out the statistical analysis and wrote the paper; Renata Kochhann supervised the data collection and was responsible for carrying out the statistical analysis and wrote the paper; Patricia Ferreira and Marina Tarrasconi collected the data and assisted with writing the article; Marcia L. Chaves and Rochele Paz Fonseca designed the study, and were responsible for the statistical design of the study, supervised the data collection, and wrote the paper.

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