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Original Research Article

Vascular Risk as a Predictor of Cognitive Decline in a Cohort of Elderly Patients with Mild to Moderate Dementia

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Key Words

Dementia · Prognosis · Aging · Aging and cognition · Alzheimer's disease

Abstract

Background/Aims: The purpose of our study was to evaluate vascular risk factors and other clinical variables as predictors of cognitive and functional decline in elderly patients with mild to moderate dementia. **Methods:** The clinical characteristics of 82 elderly patients (mean age 79.0 ± 5.9 years; 67.1% females) with mild to moderate dementia were obtained at baseline, including years of education, Framingham Coronary Heart Disease Risk score, Hachinski Ischemic Score (HIS), Clinical Dementia Rating (CDR), Mini-Mental State Examination (MMSE) score, Functional Activities Questionnaire (FAQ) score, Burden Interview Scale score, and Neuropsychiatric Inventory (NPI) score. Changes in MMSE and FAQ scores over time were assessed annually. The association between baseline clinical variables and cognitive and functional decline was investigated during 3 years of follow-up through the use of generalized linear mixed effects models. **Results:** A trend was found towards steeper cognitive decline in patients with less vascular burden according to the HIS ($\beta = 0.056$, $p = 0.09$), better cognitive performance according to the CDR score ($\beta = 0.313$, $p = 0.06$) and worse caregiver burden according to the Burden Interview Scale score ($\beta = -0.012$, $p = 0.07$) at baseline. **Conclusion:** Further studies with larger samples are necessary to confirm and expand our findings.

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Introduction

Given the interindividual variability in the progression rate of Alzheimer's disease (AD) [1] and the known poor functional performance and survival in subjects with rapid clinical progression [2, 3], there is an increasing interest in the identification of prognostic factors that may guide the implementation of targeted interventions to slow disease progression. Despite the consistent findings in previous studies on the value of worst basal cognitive performance, higher education, and younger age at diagnosis as predictors of steeper cognitive and functional decline in patients with dementia [4–8], there is still a lack of data on the role of factors amenable to intervention, such as vascular risk factors. Although cardiovascular risk has been associated with cognitive decline in neurologically healthy individuals and in patients with mild cognitive impairment [9, 10], its influence on individuals with already established dementia is still controversial and associated with inconsistent findings across different cohorts [7, 11, 12]. The primary purpose of this cohort study was to evaluate vascular risk as a predictor of cognitive and functional decline in elderly patients with mild to moderate dementia.

Materials and Methods

Study Design and Participants

Participants were followed at the Cognitive Disorders Reference Center (CEREDIC) of the University of São Paulo Medical School, Brazil, and clinically evaluated for the first time from January 1, 2005, to December 31, 2010. In this retrospective cohort study, we included all those patients who met the following criteria: diagnosis of dementia based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders IV Text Revision (DSM-IV-TR) [13]; mild to moderate severity (characterized by a Clinical Dementia Rating, CDR [14], = 1 or 2 and a Mini-Mental State Examination, MMSE [15], score >10); availability of appropriate medical records of all relevant data for the present study regarding the initial evaluation and follow-up; and age ≥ 60 years. The following exclusion criteria were applied: delirium; serious psychiatric illness, such as schizophrenia and alcohol or illicit drug abuse; severe neurological disease, such as tumor, hydrocephalus, epilepsy, Parkinson's disease, chronic subdural hematoma and traumatic brain injury; decompensated clinical or metabolic comorbidity, such as acute infection with systemic involvement, exacerbated chronic obstructive pulmonary disease, acute exacerbation of chronic kidney disease, uncontrolled thyroid disease, decompensated heart disease and liver disease with encephalopathy; other potentially reversible causes of dementia, such as vitamin B₁₂ deficiency and the use of anticholinergic drugs; and loss to follow-up before the first annual reassessment.

This study received approval from the local Committee for Ethics and Research.

Demographic and Clinical Variables

All patients were evaluated by a team of neurologists, geriatricians, and psychiatrists through a comprehensive protocol for initial and periodic follow-up care and may also have had neuropsychological, speech therapist, occupational therapist, and nursing evaluations, whenever necessary.

The minimum protocol included epidemiological data obtained from the patient and the primary caregiver, the clinical, neurological and psychiatric history, detailed clinical and neurological examination, cognitive assessment using the MMSE (range 0–30; a higher score indicating better cognition) and CDR (range 0–3; a higher rating indicating worse cognition), functional performance assessment with the Functional Activities Questionnaire (FAQ; range

0–30; a higher score indicating worse functional performance) [16], caregiver burden assessment with the Burden Interview Scale [17] (range 0–88; a higher score indicating a higher caregiver burden), neurovascular risk assessment with the Hachinski Ischemic Score (HIS; range 0–18; a higher score indicating a higher vascular burden) [18], behavior and psychological symptoms assessment with the Neuropsychiatric Inventory (NPI; range 0–144; a higher score indicating worse behavior and psychological symptoms) [19], and laboratory and neuroimaging examinations for a general clinical assessment, differential diagnosis, and exclusion of secondary causes of dementia.

We used the criteria of the working group formed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) [20] for the diagnosis of possible or probable AD, the criteria of the working group formed by the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) [21] for the diagnosis of vascular dementia, the criteria of the Consortium on Dementia with Lewy Bodies [22] for the diagnosis of dementia with Lewy bodies, and the criteria of Neary et al. [23] for the diagnosis of frontotemporal lobar degeneration.

Data concerning age, gender, systolic blood pressure, total cholesterol level, high-density lipoprotein cholesterol level, use of antihypertensive drugs, smoking and glycemic profile were extracted to generate the Framingham Coronary Heart Disease Risk (FCHDR) score, a summary index that synthesizes a combination of different vascular risk factors [24, 25] and has been used in the study of cognitive decline [9]. This score is especially suitable for populations with several overlapping risk factors [26] and, similar to the HIS, represents a comprehensive and objective measure of vascular burden to be accounted for in statistical analyses. The FCHDR score calculated for each subject was then used to classify subjects into 3 groups according to their vascular risk: low vascular risk (<10%); medium vascular risk (10–20%); and high vascular risk (>20%). Patients >80 years had their scores calculated as if they were aged 80 years old.

All data relevant to this study were obtained from chart reviews, including information regarding the initial evaluation and follow-up of each patient until the occurrence of loss to follow-up, death, referral to ambulatory care specialized in advanced cognitive impairment or completion of 3 years of follow-up.

Statistical Analyses

The baseline characteristics of the participants are given as means and standard deviations for continuous data and as percentages for categorical data. The main analysis was conducted using generalized linear mixed effects models with random intercept and slopes to determine the association of baseline predictors with changes in the MMSE and FAQ scores during the 3 years of follow-up. Baseline predictors were years of education, FCHDR score, HIS, CDR, MMSE score (only for FAQ), FAQ score (only for MMSE), Burden Interview Scale score, and NPI score. The change in the outcomes by each predictor over time was calculated by the introduction of an interaction term between the predictor and time. Models were adjusted for age and sex. Analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, N.C., USA). All *p* values were 2-sided and statistical significance was evaluated at the 0.05 level.

Results

Enrollment information is summarized in figure 1. From January 1, 2005, to December 31, 2010, 296 subjects were referred to CEREDIC for cognitive evaluation. Among them, 150 did not fulfill the inclusion criteria: 101 were diagnosed with conditions other than dementia;

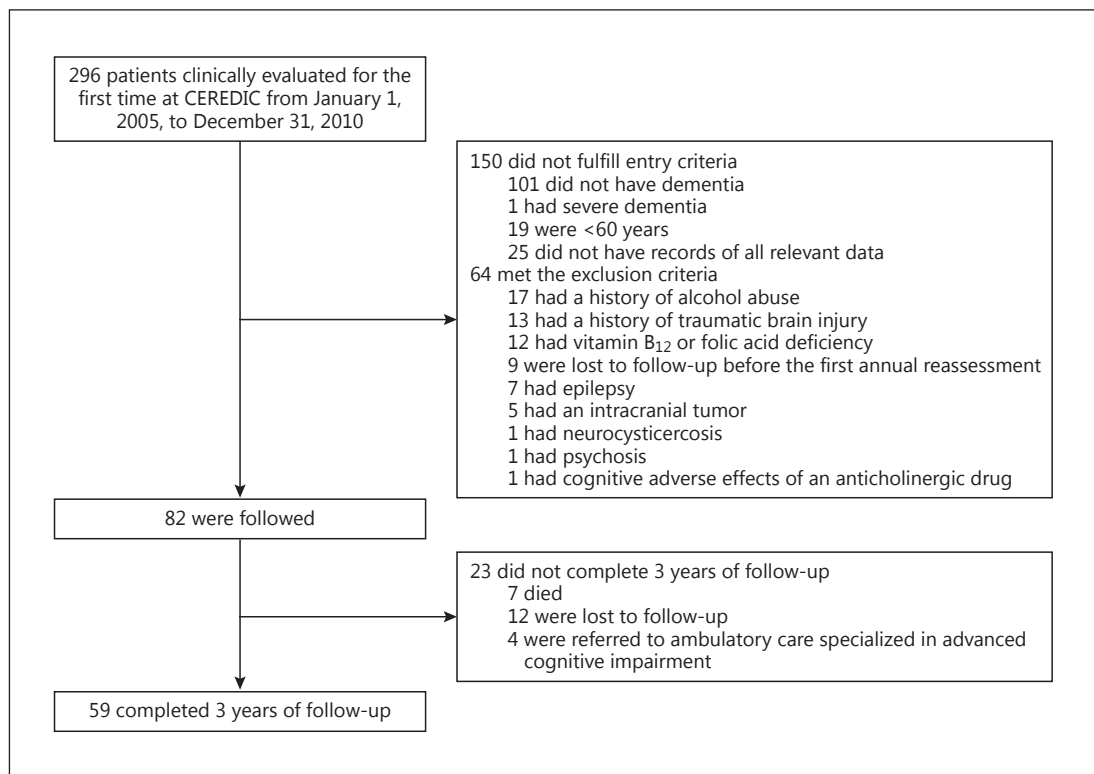


Fig. 1. Flow chart of study participants.

1 had severe dementia; 19 were <60 years; and 25 did not have appropriate medical records of all relevant data regarding the initial evaluation and follow-up (a few patients did not fulfill more than one inclusion criteria). Of the 146 remaining subjects, 64 met the exclusion criteria: 17 had a history of alcohol abuse; 13 had a history of traumatic brain injury; 12 had vitamin B₁₂ or folic acid deficiency; 9 were lost to follow-up before the first annual reassessment; 7 had epilepsy; 5 had an intracranial tumor; 1 had neurocysticercosis; 1 had psychosis; and 1 had cognitive adverse effects of an anticholinergic drug during the first evaluation (a few patients fulfilled more than one exclusion criteria). Finally, a sample of 82 subjects was followed for a mean of 3.2 ± 1.8 years. Fifty-nine subjects completed 3 years of follow-up, whereas 7 died, 12 were lost to follow-up, and 4 were referred to ambulatory care specialized in advanced cognitive impairment between the first and the third annual reassessments.

Baseline demographic and clinical characteristics of the final study sample ($n = 82$) are provided in table 1. Overall, the mean age was 79.0 ± 5.9 years, 67.1% were females, the mean years of education was 5.2 ± 4.5 , 36.6% were receiving pharmacological treatment for dementia, 41.5% had a family history of dementia, 35.4% had cerebral infarction on neuroimaging, 53.7% had high vascular risk according to the FCHDR score, 51.2% had probable AD, the mean MMSE score was 19.6 ± 4.2 , 58.5% had mild dementia, the mean FAQ score was 14.2 ± 7.0 , the mean HIS was 5.5 ± 3.4 , the mean Burden Interview Scale score was 23.9 ± 15.0 and the mean NPI score was 24.2 ± 19.9 .

We found no statistically significant associations of baseline characteristics with change in cognition and functional performance over 3 years of follow-up. Nevertheless, trends were found towards steeper cognitive decline in patients with less vascular burden according to

Table 1. Baseline demographic and clinical characteristics of the study sample (CEREDIC, n = 82)

Age, years	79.1 ± 5.9
Sex	
Male	32.93
Female	67.07
Years of education	5.2 ± 4.5
Treatment for dementia	
Anticholinesterase inhibitors	34.15
Memantine	2.44
Medical history	
Hypertension	76.83
Diabetes mellitus	20.73
Dyslipidemia	56.10
Coronary heart disease	19.51
Cerebrovascular disease	37.80
Peripheral artery disease	2.44
Current smoking	7.32
Previous smoking	24.39
Family history of dementia	41.46
Cerebral infarction on neuroimaging	35.36
Vascular risk according to the FCHDR score	
Low	6.1
Medium	40.2
High	53.7
Etiological classification according to clinical criteria	
Probable AD	51.2
Possible AD	1.2
Mixed dementia	30.4
Vascular dementia	9.7
Frontotemporal lobar degeneration	4.9
Dementia with Lewy bodies	2.4
MMSE score ^a	19.6 ± 4.2
CDR ^b	
0.5	18.3
1	58.5
2	23.2
FAQ score ^c	14.2 ± 7.0
HIS ^d	5.5 ± 3.4
Burden Interview Scale score ^e	23.9 ± 15.0
NPI score ^f	24.2 ± 19.9

^a Range 0–30; a higher score indicating better cognition.

^b Range 0–3; a higher rating indicating worse cognition.

^c Range 0–30; a higher score indicating worse functional performance.

^d Range 0–18; a higher score indicating higher vascular burden.

^e Range 0–88; a higher score indicating higher caregiver burden.

^f Range 0–144; a higher score indicating worse behavior and psychological symptoms.

the HIS ($\beta = 0.056$, $p = 0.09$), better cognitive performance according to the CDR ($\beta = 0.313$, $p = 0.06$) and worse caregiver burden according to the Burden Interview Scale score ($\beta = -0.012$, $p = 0.07$) at baseline. Additionally, another trend was found towards steeper functional decline in patients with better cognitive performance according to the CDR ($\beta = -0.810$, $p = 0.08$) at baseline (table 2).

Table 2. Association of baseline education, indices of vascular risk and scales of cognition, functional performance, caregiver burden and neuropsychiatric symptoms with change in cognition or functional performance over 3 years (CEREDIC, n = 82)

Baseline characteristics	Change in the MMSE score		Change in the FAQ score	
	β (95% CI)	p value	β (95% CI)	p value
Years of education	-0.032 (-0.078; 0.014)	0.17	-0.035 (-0.163; 0.092)	0.58
FCHDR score	0.006 (-0.008; 0.020)	0.39	-0.021 (-0.059; 0.017)	0.28
HIS	0.056 (-0.009; 0.122)	0.09	0.090 (-0.269; 0.089)	0.32
CDR	0.313 (-0.017; 0.642)	0.06	-0.810 (-1.719; 0.099)	0.08
MMSE score	NA	NA	0.029 (-0.108; 0.167)	0.68
FAQ score	0.014 (-0.018; 0.045)	0.39	NA	NA
Burden Interview Scale score	-0.012 (-0.026; 0.001)	0.07	-0.006 (-0.044; 0.032)	0.77
NPI score	0.002 (-0.013; 0.009)	0.71	-0.003 (-0.033; 0.026)	0.82

Data were adjusted for age and sex. NA = Not assessed.

Discussion

We investigated the association of vascular risk indices with changes in cognition and functional performance in a sample of elderly patients with mild to moderate dementia followed for a mean of 3.2 years. We found a trend towards steeper cognitive decline in patients with less vascular burden according to the HIS, better cognitive performance according to the CDR, and worse caregiver burden according to the Burden Interview Scale score at baseline and a trend towards steeper functional decline in patients with better cognitive performance according to the CDR at baseline.

Certain well-established risk factors for the development of dementia, such as low education [27, 28] and older age [29], have been identified in prognostic studies as predictors of better clinical outcome in patients with established dementia [5–8]. In this context, we believe that vascular risk can also have this paradoxical effect, which would explain our finding of an association between higher HIS, as a marker of cerebrovascular risk, and less cognitive decline. Indeed, it is possible that the optimized management of vascular risk factors in patients with a greater burden of cerebrovascular disease could allow greater cognitive stability compared to patients with a greater burden of neurodegeneration [30]. In addition to the low statistical power, the lack of an association between baseline FCHDR scores and cognitive and functional decline might have been due to a ceiling effect, as a high percentage of the study sample was classified as having high cardiovascular risk. Further studies are needed for the comparison of HIS and FCHDR scores as markers of vascular risk and burden in patients with dementia.

The association found in our study between better cognition at baseline and steeper cognitive and functional decline over 3 years of follow-up contrasts with the results of previous studies, in which demented patients with greater cognitive impairment at baseline were found to undergo more rapid progression of the disease [4–6]. We believe that the low education of our population, which could be interpreted as a marker of lower cognitive reserve [31], might be associated with an increased vulnerability to the effects of neurodegeneration and cerebrovascular disease, even in the early stages of dementia [32]. This low cognitive reserve could also explain the lack of association between years of education and disease progression in our sample, although a lack of statistical power could also have contributed.

Our finding of a trend for an association between worse caregiver burden at baseline and cognitive decline during follow-up is, to the best of our knowledge, unprecedented. Therefore, it should be interpreted as hypothesis generating and needs to be confirmed in future studies with larger samples.

The present study had methodological limitations that warrant caution in the interpretation of its results. We used a retrospective cohort design in which the data were collected from past records. Nevertheless, the systematic protocol of evaluation and follow-up at CEREDIC allowed us to have access to high-quality data to study prognostic factors in mild to moderate dementia in elders. Another limitation was the small sample due to the number of non-demented individuals who were referred to CEREDIC and also due to our stringent exclusion criteria. However, we believe that this stringent enrollment protocol favors better applicability of our results to patients with neurodegenerative and vascular dementias. Last, due to the retrospective design, details about the management of cardiovascular risk and neuropsychiatric symptoms during follow-up were not available; therefore, the effect of interventions on these variables on our outcomes could not be evaluated.

In summary, the present investigation provided novel data on the association between baseline vascular burden, cognitive performance and caregiver burden with cognitive decline in elderly patients with mild to moderate dementia. Further studies with larger samples of elderly individuals with dementia will be necessary to confirm and expand our findings.

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Disclosure Statement

The authors declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work, and no other relationships or activities that could appear to have influenced the submitted work.

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