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The association between cardiovascular risk factors and progressive hippocampus volume loss in persons with Alzheimer's disease

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Abstract

Background—We performed the current study to test the hypothesis that the aggregation of cardiovascular risk factors in patients with Alzheimer's disease (AD) was associated with a higher rate of volume loss in the hippocampus and progression of cognitive deficits.

Methods—A total of 103 persons with AD were included (65 men and 38 women, average age of 74.5 ± 0.8 years). All participants underwent 1.5 T structural magnetic resonance imaging (MRI), at specified intervals (6 or 12 months) for 2–3 years. We determined the rates of hippocampus, whole brain, ventricle, middle temporal lobe, fusiform, and entorhinal volume loss (in cubic millimeter/year) for all patients with AD, separately for 0–6 months, 6–12 months and 0–12, 12–18 and 18–24 months scan intervals.

Results—There were significant differences in Mini-Mental State Examination (MMSE) (p = 0.001) and Alzheimer's disease Assessment Scale (ADAS) (p = 0.01) scale scores between persons with and without hypertension and in MMSE (p = 0.04) and Clinical Dementia Rating (CDR) (p = 0.008) scale scores between persons with and without hyperlipidemia. There were no significant differences in MMSE, ADAS, and CDR scales scores between persons with and without diabetes mellitus and cigarette smoking. There were no significant differences in regional brain volume loss in those with or without cardiovascular risk factors.

Conclusions—Cardiovascular risk factors have a significant influence on the progression of cognitive deficits in patients with AD. The progression of cognitive deficits in patients with AD is not mediated by progressive hippocampal volume loss.

Keywords

Alzheimer's disease; cardiovascular risk factors; hippocampus volume loss; magnetic resonance imaging

Introduction

Alzheimer's disease (AD), the most common cause of dementia, is a progressive neurodegenerative condition, characterized histologically by the presence of neurofibrillary tangles and neuritic amyloid plaques [1]. These microscopic changes are accompanied by progressive brain volume loss, which has been demonstrated in vivo by using volumetric magnetic resonance imaging (MRI) [2]. The emergence of potentially disease-modifying therapies for AD has made both early diagnosis and monitoring of disease progression increasingly important [3].

The risk of Alzheimer disease (AD) increases with the number of cardiovascular risk factors [4–7]. We performed the current study to test the hypothesis that the aggregation of cardiovascular risk factors in patients with AD was associated with higher rate of volume loss in hippocampus and progression of cognitive deficits.

Materials and methods

We analyzed clinical and neuroimaging data collected as part of Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI) which included individuals with AD recruited at approximately 50 sites in the United States and Canada. We included all patients with AD who had a baseline and two or more followup MRI scans.

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Table 1. The serial cognitive assessments of AD participants with and without cardiovascular risk factors.

Variable	MMSE Score			ADAS Score			CDR Score		
	At baseline	At 24 months	Estimated % decrease from the baseline	At baseline	At 24 months	Estimated % increase from the baseline	At baseline	At 24 months	Estimated % increase from the baseline
Hypertension									
Presence	23.4±0.4	15.7±0.9	32.7±3.8	18.8±1.2	34±2	91.5±10.5	4.2±0.3	8.9±0.7	116.6±24.6
Absence	23.6±0.4	20.7±1	12.1±4	16.3±0.9	25.42.6±	56.2±9.6	4.2±0.4	7.6±0.9	89.7±21.2
p value	0.7	**0.001**	**0.001**	0.1	**0.01**	**0.04**	0.9	0.3	0.4
Hyperlipidemia									
Presence	23±0.4	16.1±1.2	30.1±4.9	18.5±0.8	31.6±2.3	75.3±14.1	4.9±0.3	9±0.9	70.2±18.6
Absence	23.6±0.5	19.8±0.9	15.7±4	17.9±1.4	28.4±3	62.2±14.7	3.6±0.2	7.5±0.8	122±24.7
p value	0.4	**0.04**	**0.04**	0.8	0.4	0.5	**0.008**	0.2	0.1
Diabetes mellitus									
Presence	20.7±3.2	31.4±4.8	61.7±28.7	22.4±0.7	18.3±2	17.8±9	4.29±0.3	7.7±1.5	78.6±34.5
Absence	18±1.9	25.1±3.8	37.9±12.4	22.7±0.7	21.9±1.9	8.4±1.2	3.9±0.5	6.6±0.9	73.4±18.9
p value	0.5	0.4	0.6	0.8	0.4	0.4	0.5	0.6	0.9
Cigarette smoking									
Presence	4.3±0.4	7.5±0.7	85.9±16.8	17.6±1.3	27.6±2.8	59.9±12.5	23.8±0.4	20.2±1.3	14.4±5.7
Absence	4±0.4	7.8±0.9	108.2±22.2	17±1.2	28.7±2.8	69.9±12.8	23.3±0.4	19.6±1.1	15.9±4.3
p value	0.6	0.8	0.4	0.7	0.7	0.6	0.4	0.7	0.8

MMSE score: mini-mental state examination scale, ADAS score:- Alzheimer's disease assessment scale, CDR score: clinical dementia rating sum-of-boxes scale (sum of individual CDS scales).

All participants underwent 1.5 T structural MRI, using standardized MRI protocol (http://www.loni.ucla.edu/ADNI/Research/Cores/index.shtml) at specified intervals (6, 12, 18, and 24 month) for 2–3 years. In this study, the MRI data came from 47 centers. Details of MRI acquisition and processing in the ADNI study are described in several publications [8,9]. We determined the rates of hippocampus, whole brain, ventricle, middle temporal lobe, fusiform, and entorhinal volume loss (in cubic millimeter/year) for all patients with AD, separately for 0–6 months, 6–12 months and 0–12, 12–18 and 18–24 months scan intervals. The rates of volume loss are also given in annualized percentage change relative to baseline.

Each subject's cognitive evaluation included: Mini-Mental State Examination (MMSE) [10] to provide a global measure of mental status. A brief evaluation of the cognitive domains affected in AD, including orientation, registration, attention, recall, language and constructional praxis was performed by the Alzheimer's disease Assessment Scale (ADAS) [11] which is the most used cognitive assessment battery in clinical dementia trials and Clinical Dementia Rating CDR) sum-of-boxes scale (sum of individual CDS scales) [12,13] to stage the severity of dementia. All subjects had their blood Apo E genotype determined.

In the statistical analysis, the *t*-test was used for two-group comparisons of the clinical and MRI variables of persons with AD with and without cardiovascular risk factors. Five percent for two tailed tests was chosen as the level of significance.

Results

A total of 103 persons with AD were included (65 men and 38 women, average age of 74.5±0.8 years) in the analysis. The serial cognitive assessments of AD participants with and without cardiovascular risk factors are shown in Table 1. There were significant differences in MMSE (p = 0.001) and ADAS (p = 0.01) scales scores between persons with and without hypertension and in MMSE (p = 0.04) and CDR (p = 0.008) scales scores between persons with and without hyperlipidemia. There were no significant differences in MMSE, ADAS, and CDR scales scores between persons with and without diabetes mellitus and cigarette smoking.

There were no significant differences between brain volume loss in various regions of brain in persons with and without cardiovascular risk factors (Table 2).

Discussion

Hippocampal dysfunction [14,15] and local white matter disconnections between the entorhinal cortex and hippocampus are implicated in the pathophysiology of AD [16–18]. Patients with AD have been shown to have a 27% hippocampal volume loss relative to the normal elderly persons [19]. The contribution of cardiovascular factors in patients with AD in promoting neuronal injury in hippocampus and medial temporal lobe has been suggested [20]. Considering the association between neurodegeneration and vascular factors, a more rigorous scientific evaluation of the correlation between these two has been recommended [4]. In a previous study, four risk factors: diabetes mellitus, hypertension, heart disease, and current cigarette smoking were associated with

Journal of Vascular and Interventional Neurology, Vol. 14

Table 2. Volume change in selected brain regions in AD participants with and without cardiovascular risk factors.

Variable	Hippocampus volume (mm^3)			Whole brain volume (mm^3)			Ventriclar volume (mm^3)		
	At baseline	At 24 months	Estimated % decrease from the baseline	At baseline	At 24 months	Estimated % decrease from the baseline	At baseline	At 24 months	Estimated % increase from the baseline
Hypertension									
Presence	5618±295	5619±295	7.1±0.8	958081±24738	924746±25262	3.5±0,7	45065±5371	53775±6210	20.8±2.3
Absence	6118±317	5760±320	6±1	983778±34085	933284±32627	5±1	44647±5383	54824±6584	23.3±3
p value	0.3	0.3	0.4	0.5	0.8	0.3	0.9	0.9	0.5
Hyperlipidemia									
Presence	5780±302	5480±351	5.7±1.6	968394±41258	905116±3651	6.3±1.9	51013±7738	63578±8701	27.7±5
Absence	5968±521	5530±540	7.9±1.2	971768±21932	930967±21667	4.2±0.5	35929±5768	44901±6689	25.8±3.6
p value	0.7	0.9	0.3	0.9	0.5	0.3	0.1	0.1	0.8
Diabetes mellitus									
Presence	6201±732	5813±746	6.6±2.6	958379±38258	895116±4651	5.3±2	45541±11240	54954±1309	21.7±5.9
Absence	5240±220	4807±249	8.4±1.4	981768±221932	910967±23667	4.1±0.3±	41671±6791	51249±7746	23.9±4
p value	0.2	0.2	0.6	0.8	0.6	0.4	0.8	0.9	0.8
Cigarette smoking									
Presence	5785±327	5345±339	8±1	985412±30170	943699±27938	4.2±0.4	39326±3812	48264±493	22.4±2.9
Absence	6166±384	5812±398	6.2±1	1011152±34670	974226±35032	3.7±0.6	49061±7383	59905±872	23.4±2.7
p value	0.5	0.4	0.3	0.5	0.5	0.5	0.3	0.3	0.8

Variable	Middle temporal volume (mm3)			Fusiform volume (mm3)			Entorhinal volume (mm3)		
	At baseline	At 24 months	Estimated % decrease from the baseline	At baseline	At 24 months	Estimated % decrease from the baseline	At baseline	At 24 months	Estimated % increase from the baseline
Hypertension									
Presence	16457±692	15103±772	8.6±1.8	14655±607	13454±569	7.8±2.3	2778182±	2485±161	9.8±2.6
Absence	18075±944	16458±1007	9.5±1.4	15303±672	14010±708	8.8±1	3018±213	2772±220	8.5±3.2
p value	0.2	0.3	0.7	0.5	0.6	0.7	0.4	0.2	0.7
Hyperlipidemia									
Presence	17041±1003	14941±944	12.4±1.7	14967±778	13516±916	10.1±2.4	2580±175	2330±228	10.5±4.6
Absence	16387±625	14997±650	8.6±1.3	14374±609	13405±580	6.7±1.8	2709±274	2629±344	4.4±2.9
p value	0.5	0.9	0.07	0.7	0.9	0.07	0.7	0.5	0.5
Diabetes mellitus									
Presence	16931±1166	15105±1093	10.9±1.8	14351±1011	13109±878	8.4±2.2	2890±318	2795±393	4.7±3.2
Absence	16792±819	15447±828	8.1±1.6	13109±878	13671±731	6.6±2.5	2266±199	2220±344	4±2.6
p value	0.9	0.7	0.3	0.8	0.6	0.7	0.2	0.4	0.9
Cigarette smoking									
Presence	17917±941	16496±984	8.1±1.5	15618±754	14471±726	7.3±1.5	2949±269	2724±208	5.9±3.3
absence	17801±907	16087±984	10±1.7	15344±813	14119±824	7.8±2.5	2942±208	2756±261	7.5±4.3
p value	0.9	0.8	0.5	0.8	0.8	0.9	0.9	0.9	0.8

a higher risk of progression of cognitive deficits in AD ($p < 0.10$) when analyzed individually [6]. The risk of progression of cognitive deficits AD increased with the number of risk factors (diabetes mellitus + hypertension + heart disease + current cigarette smoking).

There were significant differences in cognitive performance between persons with and without hypertension and/or hyperlipidemia. These findings provide evidence that cardiovascular risk factors significantly influence the progression of cognitive deficits in patients with AD. There were no significant differences in brain regional volumes between those with and without cardiovascular risk factors. In particular, the rate of hippocampal volume loss was not different in patients with cardiovascular risk factors such as diabetes mellitus, hypertension, heart disease, and current cigarette smoking. Therefore, the progression of cognitive deficits in patients with AD did not appear to be mediated by progressive hippocampal volume loss.

The major limitations of our work were that 2-year followup may be too short an interval to detect the progression of AD by measurement of cognitive function in patients with AD. Furthermore, we were unable to assess the adequacy of control of these cardiovascular risk factors in AD patients. Progression of cognitive deficits in AD patients with either hypertension or hyperlipidemia was not associated with volume loss in hippocampus. Other potential mechanisms may need to be investigated for progression of cognitive deficits in patients with hypertension and hyperlipidemia.

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