

Observational Study of Clinical and Functional Progression Based on Initial Brain MRI Characteristics in Patients with Alzheimer's Disease

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Abstract.

Background: Magnetic resonance imaging (MRI) is a useful tool to predict the diagnosis and progression of Alzheimer's disease (AD), especially for primary physicians. However, the correlation between baseline MRI findings and AD progression has not been fully established.

Objective: To investigate the correlation between hippocampal atrophy (HA) and white matter hyperintensities (WMH) on initial brain MRI images and the degree of cognitive decline and functional changes over 1 year.

Methods: In this prospective, 12-month observational study, dementia outpatients were recruited from 29 centers across South Korea. Baseline assessments of HA and WMH on baseline brain MRI were derived as well as cognitive function, dementia severity, activities of daily living, and acetylcholinesterase inhibitor (AChEI) use. Follow-up assessments were conducted at 6 and 12 months.

Results: Among 899 enrolled dementia patients, 748 were diagnosed with AD of whom 654 (87%) were taking AChEIs. Baseline WMH showed significant correlations with age, current alcohol consumption, and Clinical Dementia Rating score; baseline HA was correlated with age, family history, physical exercise, and the results of cognitive assessments. Among the AChEI group, changes in the Korean version of the Instrumental Activities of Daily Living (K-IADL) were correlated with the severity of HA on baseline brain MRI, but not with the baseline severity of WMH. In the no AChEI group, changes in K-IADL were correlated with the severity of WMH and HA at baseline.

Conclusion: Baseline MRI findings could be a useful tool for predicting future clinical outcomes by primary physicians, especially in relation to patients' functional status.

Keywords: Atrophy, brain imaging, cognitive function, hippocampus, white matter hyperintensities

INTRODUCTION

Structural magnetic resonance imaging (MRI) is considered a low-risk imaging technique and has been used to examine longitudinal changes in brain morphology in various neurodegenerative diseases, including dementia and Alzheimer's disease (AD) [1]. Many studies have shown MRI data on white matter and regional atrophy (medial temporal lobe structures including the hippocampus) in patients with dementia in comparison with age-matched controls, as reviewed elsewhere [2, 3].

Investigations into the correlations between brain MRI findings and various clinical markers of dementia, such as cognitive function, cerebrospinal fluid (CSF), and blood-based biomarkers, have shown variable results [4–7]. A variety of biomarkers have

been used to predict the diagnosis and progression of dementia; however, many of these markers are difficult or costly for primary physicians to assess. In the absence of simple biomarkers with prognostic utility in AD, baseline brain MRI findings, when used in combination with clinical measures, may be useful for predicting the progression of dementia or for tracking the effect of acetylcholinesterase inhibitor (AChEI) use [8–10].

In this large, prospective, observational study, we examined the correlations between baseline brain MRI parameters and clinical measures of cognitive function over a 12-month period. The aim of this study was to determine a means of predicting the degree of clinical symptom deterioration after 1 year, based on initial baseline MRI findings.

MATERIALS AND METHODS

Patients and study design

In this prospective, 12-month observational study, consecutive patients (1000 planned) with dementia were recruited from 29 centers across South Korea, between April 2014 and November 2015.

Ethical approval for the study was obtained from the local institution ethics committees, and the study was performed in accordance with principles consistent with the Declaration of Helsinki. All patients provided written informed consent prior to screening.

Patients were enrolled in the study if they met the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for dementia (including dementia resulting from AD, vascular dementia, Parkinson's disease, or Lewy body dementia, all of which were diagnosed according to DSM-IV). Additional inclusion criteria included a Korean Mini-Mental State Examination (K-MMSE) [11, 12] score ≤ 26 , available brain MRI data within 6 months of the screening visit, and consent to participate and for the use of medical data. Patients who were unable to attend scheduled study visits, had severe aphasia, had a hearing or vision disorder that meant they could not undergo the cognitive test, or were participating in any other interventional clinical trial were excluded. In this analysis, only data from patients with diagnoses of AD were included.

Assessments

At baseline, patients' demographic data, such as sex, weight, education, and family history of dementia were recorded. We also asked patients if they exercised regularly and recorded responses to 'no', 'yes, \leq twice a week', and 'yes, \geq three times a week'. Data on disease characteristics, including diagnosis, dementia type, severity, and disease duration, were also collected. MRI data were collected for the analysis of hippocampal atrophy (HA) and white matter hyperintensities (WMH).

The differentiation of vascular dementia from AD was confirmed using the National Institute of Neurological Disorders and Stroke – the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia [13] and the Hachinski Ischemic Score (HIS) [14]. Cognitive function was assessed by performance on the K-MMSE [12], and dementia severity was assessed by the Clinical Dementia

Rating (CDR) and CDR-sum of boxes (CDR-SB) scores [15, 16]. Activities of daily living (ADL) were assessed using the Korean version of the Instrumental Activities of Daily Living (K-IADL) and the Barthel ADL index scale scores [17, 18]. The K-IADL comprises 11 items that were selected by the Representative Committee of the Korean Dementia Research Group: 1) shopping, 2) mode of transportation, 3) ability to handle finances, 4) undertake housekeeping, 5) food preparation, 6) phone use, 7) responsibility for own medication, 8) recent memory, 9) hobbies, 10) television viewing, and 11) ability to fix things around the house. Each item was rated as follows: 0 = normal; 1 = with some assistance; 2 = with much assistance; 3 = unable to do; and NA = not applicable, with the final score calculated as the mean score for the 11 items excluding NA responses. The Barthel ADL scale uses 10 items to measure performance of activities of personal care and mobility.

Follow-up assessments for cognitive function, dementia severity, ADL, and concomitant use of AChEIs were conducted at 6 and 12 months.

Brain MRI

At baseline, MRI data were obtained for analysis (HA and WMH) from a scan taken within 6 months prior to baseline. Further 1.5-tesla (1.5 T) images were obtained. These were taken parallel to the anterior commissure (AC)-posterior commissure (PC) line. Mandatory images were axial images of T1, T2-FLAIR, and T2, and optional images were T1-coronal and gradient echo (GRE) imaging. The severity of WMH was evaluated according to the criteria used in the nationwide multicenter study of dementia by the Clinical Research Center for Dementia of South Korea (CREDOS). Periventricular white matter (PWM) lesions were classified as P1, P2, or P3, by cap and band < 5 mm, cap or band ≥ 5 mm and < 10 mm, and cap or band ≥ 10 mm, respectively. Deep white matter lesions were classified as D1, D2, or D3, indicating a maximum DWM lesion diameter of < 10 mm, ≥ 10 mm but < 25 mm, and ≥ 25 mm, respectively. Combinations of lesions D1 with P1 (D1P1) and D1 with P2 (D1P2) were classified as minimal. D2P1, D3P1, D2P2, D3P2, D1P3, and D2P3 combinations were classified as moderate, while D3P3 was classified as severe [19, 20]. The severity of HA was evaluated according to the axial visual rating scale for medial temporal atrophy (MTA), and they are as follows: A' is the

width of the medial temporal lobe (comprising the hippocampus-parahippocampal gyrus); C' represents the perimesencephalic cistern (PC) gap; and D' is the width of the anterior temporal horn (TH). The axial-MTA scale ranged from 0 (no atrophy) to 4 (severe atrophy): Grade 0, no MTA change without widening of the PC/TH and a normal medial temporal cortex; Grade 1, questionable atrophy of the medial temporal lobe with slight widening of the PC or slit-like TH; Grade 2, mild but definite change of the MTA, showing mild widening of the PC combined with mild but definite widening of the TH; Grade 3, moderate change of the MTA, and moderate widening of PC/TH with bending of the hippocampus proper; and Grade 4, severe change of the MTA, showing severe widening of the PC/TH with marked angulation by knife-edge change of the medial temporal cortex [21].

Outcome measures

The primary endpoint of the study was the change in ADL according to the level of white matter change on brain MRI. Secondary endpoints were the changes in cognitive function according to the level of white matter change on brain MRI, in ADL (K-IADL and Barthel ADL), and in cognitive function, according to the level of hippocampal atrophy on brain MRI. The correlations of brain MRI results, ADL (K-IADL and Barthel ADL), and cognitive function with concomitant AChEI use, and the correlation between brain MRI changes and worsening of clinical symptoms of dementia were also assessed.

Statistical analysis

Descriptive statistics were calculated for demographic and clinical characteristics such as age, sex, weight, and clinical and family history. For continuous data, the number of patients, mean, and standard deviation were calculated, while frequency and percentage were calculated for categorical data. For the primary endpoint, descriptive statistics (number of patients, mean, and standard deviation) were determined for the change in K-IADL and the results of other tests (K-MMSE, CDR, CDR-SB, and Barthel ADL) according to the degree of changes in WMH on brain MRI (classified on a visual rating scale as minimal, moderate, or severe). Differences between the groups at baseline, 6 months, and 12 months were analyzed by repeated-measures analysis of covariance (ANCOVA) with age, education, and sex as covariates. For the secondary endpoints, descriptive

statistics were calculated for the change in K-IADL or other test (as above) according to the degree of HA on brain MRI, rated on a 5-point visual rating scale scored from absent (0) to severe (4). The raters were Hojin Kim (Hanyang University Guri Hospital) and Youngsoon Yang (VHS Medical Center), and both were blinded to the patient data. The changes between the groups at baseline, 6 months, and 12 months were compared by repeated-measures ANCOVA with age, education, and sex as covariates. For the analysis of K-IADL according to AChEI use, descriptive statistics were calculated for continuous data and the frequency and percentage were calculated for categorical data. The differences between the groups at baseline, 6 months, and 12 months were also compared by repeated-measures ANCOVA with age, education, and sex as covariates. To identify risk factors for WMH and HA on brain MRI, demographic and clinical characteristics were investigated by multiple logistic regression analysis. All differences were considered statistically significant at $p < 0.05$. Data were analyzed with SPSS version 18.0 for Windows (SPSS, Chicago, IL).

RESULTS

Patient disposition and characteristics

A total of 899 patients with dementia were enrolled (Table 1). Of these, 83.2% ($n = 748$) had a diagnosis of dementia related to AD; this group comprised the analysis set in the present study. Other diagnoses included vascular dementia (11.8%), Parkinson's disease (3.5%), Lewy body dementia (1.3%), and mild cognitive disorders or atypical dementia (0.2%); these patients were not included in the analysis. Demographic and baseline characteristics of the analysis set are presented in Table 1. The mean age of these patients was 75 years, and 55% were female (Table 1). The majority of patients were treated as outpatients and had no family history of dementia or stroke. Most patients were taking concomitant AChEIs ($n = 654$, 87.4%): 553 (73.9%) were receiving donepezil, and 101 (13.5%) were receiving rivastigmine. Some patients ($n = 94$) were not taking, or declined to take, any AChEIs because of the side effects.

Risk factors for WMH and HA

In this study, the inter-rater reliabilities for WMH and right and left HA combined were 91.80%

(K=0.8840) and 95.76% (K=0.9435) agreement, respectively. According to multiple logistic regression analysis, age, current alcohol consumption, and higher CDR score were correlated with more severe WMH in baseline MRI (Table 2). Age, presence of

dementia in family history, physical exercise, and the results of cognitive assessment were correlated with HA severity in multiple regression analysis (Table 3).

Changes in cognitive functions were not correlated with the severity of WMH on baseline brain MRI

The change in K-IADL, according to the degree of WMH on brain MRI from baseline, was not significant at 6 or 12 months (Table 4). Likewise, changes in K-MMSE, CDR, CDR-SB, and Barthel ADL according to the degree of WMH were not significant at 6 or 12 months.

Changes in K-IADL, but not other cognitive functions, correlated with the severity of HA on baseline brain MRI

The change in K-IADL, according to the degree of right HA on brain MRI from baseline, was significant at 12 months ($p=0.0323$, repeated-measures ANCOVA) but not at 6 months ($p=0.2152$, repeated-measures ANCOVA) (Table 4). The change in K-IADL, according to the degree of left HA on brain MRI from baseline, was also significant at 12 months ($p=0.0477$, ANCOVA), but not at 6 months ($p=0.2345$, repeated-measures ANCOVA). However, changes in K-MMSE, CDR, CDR-SB, and Barthel ADL, according to the degree of right or left

Table 1

Patient (analysis set) demographics and baseline characteristics (n = 748)

Characteristics		n (%)
Age (y)	Mean ± SD	75.03 ± 7.50
Sex	Male	366 (44.92)
	Female	412 (55.08)
Weight (kg)	Mean ± SD	58.25 ± 9.39
Education (y)	Mean ± SD	5.62 ± 5.04
K-MMSE	Mean ± SD	19.68 ± 5.05
CDR	Mean ± SD	0.96 ± 0.50
CDR-SB	Mean ± SD	5.45 ± 2.87
K-IADL	Mean ± SD	0.99 ± 0.71
Barthel ADL	Mean ± SD	18.86 ± 2.59
Dementia	Yes	86 (11.50)
Family history	No	662 (88.50)
Stroke	Yes	99 (13.24)
Family history	No	649 (86.76)
Physical exercise (Activity)	No	396 (52.94)
	Yes (≤2 times a week)	198 (26.47)
	Yes (≥3 times a week)	154 (20.59)
Smoking status	Never smoked	594 (79.41)
	Still smoking	42 (5.61)
	Previous smoker	112 (14.97)
Current alcohol consumption	Yes	138 (18.45)
	No	610 (81.55)

Barthel ADL, Barthel Activities of Daily Living Index; CDR, Clinical Dementia Rating scale; CDR-SB, CDR-sum of boxes; K-IADL, Korean Instrumental Activities of Daily Living; K-MMSE, Korean Mini-Mental State Examination.

Table 2

Multiple logistic regression analysis of factors associated with the severity of white matter change

Factor		Estimate	SE	Odds Ratio [95% CI]	p
Age		0.0410	0.0112	1.042 [1.019, 1.065]	0.0003
Sex	Female (1) versus Male (0)	0.1101	0.1936	1.116 [0.764, 1.632]	0.5695
Weight		0.0217	0.0254	1.022 [0.972, 1.074]	0.3929
Education	Beyond elementary school graduation (1) versus elementary school graduation or less (0)	-0.1212	0.1757	0.886 [0.628, 1.250]	0.4905
Dementia family history	Yes (1) versus No (0)	-0.1658	0.2486	0.847 [0.520, 1.379]	0.5048
Stroke family history	Yes (1) versus No (0)	0.3181	0.2270	1.375 [0.881, 2.145]	0.1612
Physical exercise	Yes (1) versus No (0)	-0.3073	0.1623	0.735 [0.535, 1.011]	0.0584
Smoking status	Still smoking (1) versus Never smoked (0)	0.2786	0.3350	1.321 [0.685, 2.547]	0.4056
	Smoked in the past, but quit (1) versus Never smoked (0)	-0.0848	0.2383	0.919 [0.576, 1.466]	0.7220
Current alcohol consumption	Yes (1) versus No (0)	0.6010	0.2170	1.824 [1.192, 2.791]	0.0056
K-MMSE		0.0022	0.0198	1.002 [0.964, 1.042]	0.9134
CDR		0.3817	0.1897	1.465 [1.010, 2.124]	0.0442
K-IADL		0.1367	0.1462	1.146 [0.861, 1.527]	0.3498
Barthel ADL		0.0501	0.0325	1.051 [0.987, 1.120]	0.1231

Barthel ADL, Barthel Activities of Daily Living Index; CDR, Clinical Dementia Rating scale; CI, confidence interval; HIS, Hachinski Ischemic Scale; K-IADL, Korean Instrumental Activities of Daily Living; K-MMSE, Korean Mini-Mental State Examination.

Table 3
Multiple logistic regression analysis of factors associated with the severity of left or right hippocampal atrophy

Left		Estimate	SE	Odds Ratio [95% CI]		<i>p</i>
Age		0.0337	0.0098	1.034	[1.015, 1.054]	0.0006
Sex	Female (1) versus Male (0)	0.1322	0.1742	1.141	[0.811, 1.606]	0.4480
Hospitalization/Outpatient	Outpatient versus Hospitalization	-0.4760	0.2584	0.621	[0.374, 1.031]	0.0655
Weight		0.0425	0.0230	1.043	[0.997, 1.091]	0.0650
Education	Over elementary school graduation (1) versus Elementary school graduation or less (0)	0.1290	0.1581	1.138	[0.835, 1.551]	0.4145
Dementia family history	Yes (1) versus No (0)	-0.5090	0.2241	0.601	[0.387, 0.933]	0.0231
Stroke family history	Yes (1) versus No (0)	0.1681	0.2079	1.183	[0.787, 1.778]	0.4187
Physical exercise	Yes (1) versus No (0)	-0.8458	0.1482	0.429	[0.321, 0.574]	<0.0001
Smoking status	Still smoking (1) versus Never smoked (0)	0.0988	0.3098	1.104	[0.601, 2.026]	0.7498
	Smoked in the past, but quit (1) versus Never smoked (0)	0.1597	0.2157	1.173	[0.769, 1.790]	0.4591
Current alcohol consumption	Yes (1) versus No (0)	0.2439	0.1990	1.276	[0.864, 1.885]	0.2204
K-MMSE		-0.0369	0.0180	0.964	[0.930, 0.999]	0.0411
CDR		0.6683	0.1747	1.951	[1.385, 2.748]	0.0001
K-IADL		-0.3193	0.1333	0.727	[0.560, 0.944]	0.0166
Barthel ADL		0.0321	0.0289	1.033	[0.976, 1.093]	0.2676
Right		Estimate	SE	Odds Ratio [95% CI]		<i>p</i>
Age		0.0369	0.0081	1.038	[1.021, 1.054]	<0.0001
Sex	Female (1) versus Male (0)	0.1917	0.1201	1.211	[0.957, 1.533]	0.1105
Hospitalization/Outpatient	Outpatient versus Hospitalization	-0.1997	0.2408	0.819	[0.511, 1.313]	0.4069
Weight		0.0086	0.0223	1.009	[0.965, 1.054]	0.6991
Education	Over elementary school graduation (1) versus elementary school graduation or less (0)	-0.2648	0.1247	0.767	[0.601, 0.980]	0.0337
Dementia family history	Yes (1) versus No (0)	-0.4399	0.1956	0.644	[0.439, 0.945]	0.0245
Stroke family history	Yes (1) versus No (0)	-0.3099	0.1801	0.733	[0.515, 1.044]	0.0852
Physical exercise	Yes (1) versus No (0)	-0.8132	0.1228	0.443	[0.349, 0.564]	<0.0001
Smoking status	Still smoking (1) versus Never smoked (0)	0.0706	0.2464	1.073	[0.662, 1.740]	0.7744
	Smoked in the past, but quit (1) versus Never smoked (0)	-0.0469	0.1679	0.954	[0.687, 1.326]	0.7801
Current alcohol consumption	Yes (1) versus No (0)	0.1598	0.1483	1.173	[0.877, 1.569]	0.2812
HIS Total score		-0.0123	0.0182	0.988	[0.953, 1.024]	0.4972
K-MMSE		-0.0696	0.0118	0.933	[0.911, 0.955]	<0.0001
CDR		0.5103	0.1124	1.666	[1.336, 2.076]	<0.0001
CDR-SB		0.0893	0.0195	1.093	[1.052, 1.136]	<0.0001
K-IADL		0.2508	0.0807	1.285	[1.097, 1.505]	0.0019
Barthel ADL		-0.0683	0.0201	0.934	[0.898, 0.972]	0.0007

Barthel ADL, Barthel Activities of Daily Living Index; CDR, Clinical Dementia Rating scale; CDR-SB, CDR-sum of boxes; CI, confidence interval; HIS, Hachinski Ischemic Scale; K-IADL, Korean Instrumental Activities of Daily Living; K-MMSE, Korean Mini-Mental State Examination.

HA on brain MRI from baseline, were not significant at 6 or 12 months.

K-IADL in the AChEI use and non-AChEI use groups according to WMH and HA on brain MRI

In the AChEI use group, the change in K-IADL, according to the degree of change in WMH on brain MRI from baseline, was not significant at 6 or 12 months. The change in K-IADL, according to the degree of right and left HA on brain

MRI from baseline, was significant at 12 months ($p=0.0319$ and $p=0.0457$, respectively; repeated-measures ANCOVA) (Table 5).

In the non-AChEI use groups, however, the change in K-IADL, according to the degree of WMH on brain MRI from baseline, was significant at 12 months ($p=0.0423$, repeated-measures ANCOVA) (Table 3). The change in K-IADL, according to the degree of right and left HA on brain MRI from baseline, was also significant at 12 months ($p=0.0297$ and $p=0.0318$, respectively; repeated-measures ANCOVA) (Table 5).

Table 4

Korean Instrumental Activities of Daily Living score changes over 1 year in relation to white matter hyperintensities/hippocampal atrophy (least-squares mean ± standard error)

White matter hyperintensities	Minimal ¹ (n = 435)		Moderate ² (n = 224)	Severe ³ (n = 89)		p ⁴
Baseline	0.97 ± 0.03		0.99 ± 0.05	1.08 ± 0.07		0.6378
6 months	1.00 ± 0.04		1.05 ± 0.05	1.09 ± 0.08		0.4785
12 months	1.00 ± 0.04		1.07 ± 0.05	1.10 ± 0.07		0.4247
Right hippocampal atrophy	0 (n = 192)	1 (n = 259)	2 (n = 161)	3 (n = 98)	4 (n = 38)	p
Baseline	0.95 ± 0.05	0.98 ± 0.04	0.97 ± 0.06	1.18 ± 0.07	1.23 ± 0.06	0.2436
6 months	0.94 ± 0.06	1.01 ± 0.05	0.99 ± 0.06	1.21 ± 0.08	1.34 ± 0.07	0.2152
12 months	0.91 ± 0.06	1.03 ± 0.05	1.04 ± 0.07	1.36 ± 0.10	1.45 ± 0.07	0.0323
Left hippocampal atrophy	0 (n = 183)	1 (n = 207)	2 (n = 184)	3 (n = 111)	4 (n = 63)	p
Baseline	0.94 ± 0.05	0.98 ± 0.05	0.98 ± 0.05	1.07 ± 0.07	1.12 ± 0.06	0.3273
6 months	0.96 ± 0.04	1.02 ± 0.06	0.97 ± 0.05	1.18 ± 0.07	1.22 ± 0.07	0.2345
12 months	0.96 ± 0.06	0.99 ± 0.06	1.02 ± 0.06	1.23 ± 0.08	1.36 ± 0.07	0.0477

Repeated-measures ANCOVA, with age, education, and sex as covariates. ¹DWM/PWM: D1P1, D1P2. ²DWM/PWM: D1P3, D2P1, D2P2, D2P3, D3P1, D3P2. ³DWM/PWM: D3P3. ⁴p-values represent the significance of differences in the change from baseline between the different severity groups, at each time point. DWM, deep white matter; PWM, periventricular white matter.

Table 5

Comparative Korean Instrumental Activities of Daily Living for acetylcholinesterase inhibitor (AChEI) use and non-AChEI use groups (white matter change, hippocampal atrophy)

	White matter hyperintensities	Minimal ¹ (n = 384)	Moderate ² to Severe ³ (n = 270)	p ⁴
Use of AChEI (n = 654)	Baseline	0.97 ± 0.03	1.02 ± 0.05	0.4316
	6 months	1.00 ± 0.03	1.04 ± 0.05	0.5121
	12 months	1.00 ± 0.04	1.06 ± 0.05	0.3322
	Right hippocampal atrophy	0-1 (n = 384)	2-4 (n = 270)	p
	Baseline	0.96 ± 0.04	1.06 ± 0.07	0.4172
	6 months	0.97 ± 0.06	1.18 ± 0.07	0.1358
	12 months	0.95 ± 0.05	1.29 ± 0.08	0.0319
	Left hippocampal atrophy	0-1 (n = 327)	2-4 (n = 327)	p
	Baseline	0.96 ± 0.05	1.05 ± 0.06	0.4221
	6 months	0.98 ± 0.05	1.16 ± 0.07	0.1915
	12 months	0.98 ± 0.05	1.25 ± 0.08	0.0457
	No use of AChEI (n = 94)	White matter hyperintensities	Minimal ¹ (n = 51)	Moderate ² to Severe ³ (n = 43)
Baseline		0.97 ± 0.02	1.04 ± 0.05	0.2158
6 months		1.00 ± 0.02	1.11 ± 0.05	0.0734
12 months		1.01 ± 0.02	1.16 ± 0.06	0.0423
Right hippocampal atrophy		0~2 (n = 67)	3-4 (n = 27)	p
Baseline		0.96 ± 0.04	1.05 ± 0.04	0.4971
6 months		0.98 ± 0.07	1.20 ± 0.07	0.1261
12 months		0.96 ± 0.06	1.30 ± 0.08	0.0297
Left hippocampal atrophy		0-2 (n = 63)	3-4 (n = 31)	p-value
Baseline		0.96 ± 0.04	1.06 ± 0.05	0.4588
6 months		0.98 ± 0.04	1.17 ± 0.06	0.2932
12 months		0.99 ± 0.05	1.28 ± 0.07	0.0318

Repeated-measures ANCOVA, with age, education, and sex as covariates. ¹DWM/PWM: D1P1, D1P2. ²DWM/PWM: D1P3, D2P1, D2P2, D2P3, D3P1, D3P2. ³DWM/PWM: D3P3. ⁴p-values represent the significance of differences in the change from baseline between the different severity groups, at each time point. DWM, deep white matter; PWM, periventricular white matter.

DISCUSSION

The results of this study indicate that the degree of WMH on baseline MRI was not associated with the deterioration in cognitive function or ADL after

12 months. However, the severity of HA on baseline MRI was significantly correlated with the deterioration of K-IADL after 1 year. In addition, the level of baseline WMH in the AChEI group was not associated with K-IADL deterioration 12 months later;

however, there was a significant association at 12 months in patients who continued to be free of AChEI use.

At present, cerebral WMH and HA are the most important biomarkers of vascular dementia and AD [1–8]. Cerebral WMH are known to increase with age, and our results were consistent with these observations [22]. A long-term study of patients with mild cognitive impairment showed that the risk of dementia was significantly increased in patients with a large amount of subcortical hyperintensities at baseline [23]. Moreover, although ADL is not only affected by cognitive function, there are conflicting results indicating that WMH do not affect cognition [24–26]. These contradictory findings can be explained by the results of a recent study showing that the WMH burden of strategic white matter tracts, such as the forceps minor or anterior thalamic radiations, are more important than a global assessment of WMH [27]. In the present study, the degree of baseline WMH correlated with CDR scores, but not with MMSE scores, and this is probably due to the evaluation of the global WMH burden using a visual rating. The results of this study suggest that baseline WMH is not associated with cognitive function and ADL deterioration after 12 months. We also suggest that, in future studies, an evaluation of WMH burden in strategic white matter tracts, such as the forceps minor or anterior thalamic radiations, may give different results. This is supported by our observations that, in patients without moderate and severe WMH on baseline MRI, there is a significant deterioration in the 1-year change in K-IADL, as was observed in the non-AChEI use group compared with the AChEI use group.

It is well known that HA on MRI is an indicator of neuronal cell degeneration in AD patients. Increased severity of HA is associated with a higher risk of progression to AD in patients with mild cognitive impairment. In this study, the severity of HA on baseline MRI correlated with the changes in cognitive function and ADL. However, the change in cognitive function over 12 months did not correlate with the degree of baseline HA; this is likely due to the fact that cognitive function was assessed only by MMSE, without a detailed neuropsychological test. However, irrespective of AChEI use, higher severity of HA at baseline correlated with worse K-IADL scores 12 months later. The purpose of this study was to allow primary physicians who do not have access to biomarkers the means to assess the degree of HA and WMH on initial MRI in order to predict the amount of deterioration of cognitive function and ADL in

patients with AD. It is also noteworthy that the severity of baseline HA in the treatment group was found to be associated with deterioration of cognitive function after 12 months, regardless of the use of AChEIs. This finding is consistent with previous studies showing that cognitive function and the response to AChEI treatment was reduced in patients with more severe baseline HA [9–10].

In this study, alcohol drinking was a significant risk factor for WMH, but smoking was not, consistent with previous research results [28]. However, there are also contradictory findings which show that smoking status correlates with changes in white matter [15, 16]. Level of physical exercise was negatively correlated with HA in this study, suggesting that physical exercise might have preventive effects against the progression of HA [17, 18].

Several biomarkers (i.e., amyloid and tau positron-emission tomography and CSF protein levels) have been investigated for their utility in the accurate diagnosis of AD [19–21, 29]. In particular, evaluation of the pathological biomarkers amyloid and tau is critical for accurate diagnosis. However, these biomarkers are not routinely assessed at all institutions. Considering that most AD patients are evaluated and treated at local hospitals, rather than large and well-equipped dementia centers, MRI plays a key role in the evaluation of AD [30, 31]. In this regard, the present study is meaningful in that the primary physician can evaluate the baseline WMH and HA by MRI, which is relatively easy to use, thus providing a basis for predicting the deterioration of function in the patient after 12 months.

A limitation of this study is that the diagnostic criteria used for AD were the DSM-IV clinical diagnostic criteria, and that cognition was assessed only by MMSE, without a detailed neuropsychological test. There is also the disadvantage that WMH was evaluated using a visual rating scale. Furthermore, only early dementia patients were recruited, and a 12-month observation period may have been too brief to determine the extent of decline in this population. Notably, this was an observational study, and there are a number of limitations associated with observational research. Thus, some discretion is required in interpreting our results.

Conclusion

The results of this study show that baseline MRI findings could be a useful tool for predicting clinical outcomes. Further research is needed to understand

the relationship between clinical symptoms and MRI findings in AD patients.

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