

# The Clinical Characteristics according to the Educational Level in the Elderly Patients with Mild Alzheimer's Disease Dementia

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**Background and Purpose** Cognitive reserve is important for the individual susceptibility to dementia. Among the various determinants of cognitive reserve, the number of years of formal education would be of prime importance. We performed this study to explore its contribution to the clinical characteristics of dementia.

**Methods** We included consecutive mild Alzheimer's disease (AD) dementia patients (clinical dementia rating, CDR=0.5 or 1) who visited our memory clinic and were older than 70 years at the evaluation from October 2013 to September 2015. According to the number of years of education, the corresponding subjects was grouped into two extreme educational groups, low education (illiterate or partially illiterate, LE,  $n=43$ ) vs. high education (more than 9 years of education, HE,  $n=34$ ). Among these patients, we compared various demographic, neuropsychological and neuroimaging characteristics.

**Results** The groups were comparable in terms of age, frequency of hypertension and diabetes, and CDR and its sum of box. However, female gender was more frequent in the LE group ( $p=0.000$ ). Also this group showed a more depressive mood on the geriatric depression scale ( $p=0.007$ ). The raw scores on Korean Version of Mini-Mental State Examination and well-validated neuropsychological tests were lower in the LE group. However, the cognitive performance was found to be more preserved in the LE group than in the HE group when assessed using the z-score in certain specified tests on univariate and multivariate analyses ( $p<0.05$ ). The Schelten's grade of medial temporal atrophy was similar between the two educational groups. Also, the degree of combined ischemic burden did not differ between the two groups.

**Conclusions** We identified that the prevalence of depressive mood and the extent of decline from the corresponding norm in a particular neuropsychological performance differ according to the educational level of mild AD patients.

**Key Words** Alzheimer's disease, cognitive reserve, education, illiteracy, neuropsychological test.

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## INTRODUCTION

The individual susceptibility to dementia including Alzheimer's disease (AD) differs. The genetic risk factor like apolipoprotein  $\epsilon 4$ , vascular risk factors, history of head trauma,

and chronic depression increase the risk of AD.<sup>1</sup> Cognitive reserve is crucial in the aspect that it decreases the individual vulnerability to dementia.<sup>2</sup> Among the various determinants of cognitive reserve, the educational level would be of prime importance because it has a high influence on the life-long socioeconomic attainments and other cognitive capacities. An individual with poor education is more likely to develop AD.<sup>3,4</sup> Illiteracy is the extreme end of low education, which was not uncommon in aged population of our country due to the specific historical situation.<sup>5</sup> It was reported to increase the

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risk of AD.<sup>3-5</sup> However, we have scanty information with respect to the clinical characteristics of AD patients who are illiterate.

To understand the clinical characteristics of dementia depending on the educational level, we performed a cross-sectional study comparing the two contrasting groups, illiterate patients vs. highly educated (more than 9 years of formal education) individuals, within the same clinical stage of mild AD dementia.

## METHODS

### Subjects

Participants were consecutively recruited for this study from October 2013 to September 2015. The routine neurological examinations, intense interviews with patients and caregivers, neuropsychological testing, and brain magnetic resonance imaging (MRI) were performed.

All the patients met the revised clinical criteria for probable AD from the National Institute on Aging-Alzheimer's Association.<sup>6</sup> We had 247 probable AD patients during this period. Among them, only the elderly subjects who were older than 70 years at the evaluation, and who were in the mild dementia stage (clinical dementia rating, CDR=0.5 or 1) were considered for this study. According to our study design that compared the two extreme educational groups, the illiterate, partially illiterate (no formal education but having the ability to read simple words), or highly educated (more than 9 years of formal education, HE) individuals, were included. Finally 77 patients were included in this study.

### Neuropsychological assessment

The scores on the short version of Geriatric Depression Scale (GDS), Barthel activities of daily living, and Korean instrumental activities of daily living<sup>7</sup> were obtained from the patients and their caregivers. Overall cognitive performance was evaluated using the Korean version of the Mini-Mental State Examination (K-MMSE),<sup>8</sup> the CDR, and CDR-sum of box (SOB).

The standardized neuropsychological tests included the Seoul Neuropsychological Screening Battery (SNSB)-II. However, for comparison between the two groups, the data from only the following tests were used; the forward digit span test which measures attention; the Rey Complex Figure Test (RCFT) which evaluates visual functioning and visual memory; the Seoul Verbal Learning Test (SVLT) which assess verbal memory; and the semantic Controlled Oral Word Association Test (COWAT) which validates executive functioning. We selected these tests because the z-scores of the tests are

delicately defined, and are thought to be less affected by illiteracy. Norms according to age, gender, and educational level were based on the data obtained from 447 normal subjects in SNSB-I,<sup>9</sup> which have been updated in SNSB-II incorporating normal data from 1100 individuals ([http://www.human-brainkorea.com/Item/Default.aspx?sub=SNSB\\_2](http://www.human-brainkorea.com/Item/Default.aspx?sub=SNSB_2)). The raw scores were converted to z-scores based on the means of the individual groups, which are determined by the difference in age, gender, and educational level. Thus, the z-score would allow accurate comparison of the test results between the subjects who differ in terms of age, gender, or educational level.<sup>10</sup> Composite z-scores were then established for the individual tests by averaging the z-transformed data of the corresponding tests. We used the composite z-scores to compare between the two groups.

### Analysis of neuroimaging data

All subjects underwent Brain MRI scan using a 3.0 Tesla MRI scanner (SignaHDxt; GE Healthcare, Waukesha, WI, USA). Coronal 3D T1-weighted images and fluid-attenuated inversion recovery (FLAIR) were used for analysis of medial temporal atrophy (MTA) and white matter ischemic burden, respectively. 3D T1 MR images were acquired with the following imaging parameters; coronal slice thickness, 1 mm; inter-slice thickness, 0 mm; the repetition time, 9.9 ms; the echo time, 4.6 ms. The parameters of FLAIR images were 750–1000/25–40/2.4 in repetition time/echo time/excitations, flip angle of 10°, and section thickness of 5 mm with a gap of 1.5 mm.

MTA was assessed using Schelten's scale which visually grades the extent of MTA from grade 0 to 4.<sup>11</sup> Because of the limitation of the number of subjects, we categorized MTA into two groups: mild (grade 1 and 2) and severe (grade 3 and 4) for statistical analysis. The severity of ischemic burden was validated using the Clinical Research Center for Dementia of South Korea Visual Rating Scale.<sup>12</sup> Briefly, periventricular ischemia was classified into P1 (cap or band <5 mm), P2 (5 mm ≤ and <10 mm), and P3 (cap or band ≥10 mm). The ischemic lesions in the deep white matter were divided into the following groups; D1 (<10 mm), D2 (10 mm ≤ and <25 mm), and D3 (≥25 mm). Further, the two ratings were combined for a final analysis as none, minimal, moderate, and severe according to the prior literature.<sup>11</sup> We did not count the number of lacunes because none of the subjects showed a lacune on FLAIR imaging.

### Statistics

Statistical analyses were conducted using SPSS Ver. 19.0 for Windows (SPSS Inc., Chicago, IL, USA). Comparisons were performed between the two groups using independent *t*-tests

for continuous variables and chi-square tests for categorical variables. Correlations between the variables were assessed using Pearson's or Spearman's correlation test. A multiple regression analysis with a stepwise procedure was performed to determine whether the variables were still significant even when the demographic covariates were considered. A *p*-value <0.05 was considered significant in all statistical tests.

## RESULTS

### The demographic characteristics

We had 43 subjects in the low education group (LE, illiterate or partially illiterate), and 34 subjects in the HE group according to our study inclusion criteria. The demographics did not reveal a difference in age, and frequency of diabetes and hypertension (Table 1). However, female gender was much more frequent in the LE group (39 vs. 9, *p*=0.000). The degree of dementia severity assessed by CDR and CDR-SOB was comparable between the two groups.

### The comparison of neuropsychological data

The LE group showed a more depressive mood on the short form of GDS (*p*=0.007) (Table 2). The raw score on K-MMSE was lower in the LE group (*p*=0.000). However, their achievement was found to be less impaired than that in patients of the HE group when assessed using the z-score on K-MMSE (*p*=0.001). Similar results were obtained which showed a lower raw score but a higher z-score on the following tests: the copy time (*p*=0.001) and immediate recall on RCFT (*p*=0.000), immediate and delayed recall, and recognition on SVLT (*p*=0.002, 0.000, 0.001, respectively), and categorical verbal fluency test of COWAT supermarket (*p*=0.025). These findings demonstrate that the cognitive decline from the premorbid state is much less in mild AD patients with LE than in subjects with HE. The impairment in activities of daily living such as self-

care and usage of instruments was similar between the two groups.

Due to the possibility of impact of depression on neuropsychological performance, we examined the correlation between GDSs score and the individual neuropsychological parameter, which was significant on univariate analysis that included all subjects. On Pearson's correlation analysis, copy time (*p*=0.903), and immediate recall on RCFT (*p*=0.433), immediate (*p*=0.817) and delayed recall (*p*=0.899), and recognition on SVLT (*p*=0.368), and COWAT supermarket (*p*=0.072) did not show a significant relationship with the depression scale.

**Table 2.** The analysis of the neuropsychological data

	LE (n=43)	HE (n=34)	<i>p</i> -value
GDSs	8.3±4.3	5.5±4.2	0.007*
B-ADL	18.0±3.6	17.9±4.3	0.908
K-IADL	6.7±3.7	4.8±2.3	0.160
K-MMSE (total)	16.8±4.4	22.9±3.6	0.000*
K-MMSE (z)	-1.9±1.1	-3.1±1.9	0.001*
Digit span (z)	-0.24±0.97 (4.0±1.1)	-0.22±0.95 (5.7±1.3)	0.929
RCFT copy (z)	-1.2±1.1 (12.7±9.2)	-1.5±2.3 (27.6±8.2)	0.477
RCFT time (z)	0.24±1.17 (267±145)	-0.79±1.32 (266±138)	0.001*
RCFT-I (z)	-0.71±0.56 (2.6±3.1)	-1.38±0.61 (6.4±4.3)	0.000*
RCFT-D (z)	-0.67±0.72 (2.8±3.9)	-1.45±0.57 (5.9±3.8)	0.447
RCFT-R (z)	-0.94±0.95 (64.2±10.5)	-1.37±1.09 (71.2±9.9)	0.071
SVLT-I (z)	-1.4±0.9 (8.4±4.1)	-2.0±0.6 (9.7±3.6)	0.002*
SVLT-D (z)	-1.1±0.7 (1.3±1.6)	-1.8±0.8 (1.6±2.0)	0.000*
SVLT-R (z)	-0.76±1.09 (70.5±11.9)	-1.7±1.1 (71.2±10.7)	0.001*
COWATa (z)	-1.0±1.2 (8.1±3.7)	-1.5±1.0 (9.3±4.6)	0.059
COWATs (z)	-0.98±0.86 (7.0±3.6)	-1.41±0.78 (8.9±4.5)	0.025*

The number in the parenthesis is the raw score on the individual test.

\**p*<0.05 is significant.

B-ADL: Barthel activities of daily living, COWATa: controlled oral word association test-animal, COWATs: controlled oral word association test-supermarket, D: delayed-recall, GDSs: short form of Geriatric Depression Scale, HE: high education group, I: immediate recall, K-IADL: Korean instrumental activities of daily living, K-MMSE: Korean Version of Mini-Mental State Examination, LE: low education group, R: recognition index, RCFT: Rey Complex Figure Test, SVLT: Seoul Verbal Learning Test, z: z-score.

**Table 1.** Demographic characteristics

	LE (n=43)	HE (n=34)	<i>p</i> -value
Age	80±5.4	79±4.9	0.218
Gender (F:M)	39:4	9:25	0.000*
Hypertension	26 (60%)	16 (47%)	0.259
Diabetes	13 (30%)	10 (29%)	1.000
CDR			0.821
0.5	23	17	
1.0	20	17	
CDR-SOB	3.5±1.8	3.4±2.0	0.919

Mean±standard deviation.

\**p*<0.05 is significant.

CDR: clinical dementia rating, F: female, HE: high education group, LE: low education group, M: male, SOB: sum of box.

**Table 3.** The analysis of the neuroimaging data

	LE (n=43)	HE (n=34)	p-value
Schelten's grade, Rt.			0.058
1 to 2	32	18	
3 to 4	11	16	
Schelten's grade, Lt.			0.639
1 to 2	28	20	
3 to 4	15	14	
Ischemic burden			0.157
None	9	2	
Minimal	9	10	
Moderate	25	22	
Severe	0	0	

HE: high education group, LE: low education group.

Further, in order to assess the persistency of the neuropsychological variables in their statistical significance even after adjusting for the demographic confounders; age, gender, and presence of hypertension and diabetes, we performed a multiple regression analysis. Depression ( $\beta=-0.374$ ,  $p=0.018$ ), z-score on K-MMSE ( $\beta=-0.331$ ,  $p=0.021$ ), copy time on RCFT ( $\beta=-0.437$ ,  $p=0.005$ ), and immediate recall on RCFT ( $\beta=-0.502$ ,  $p=0.001$ ) and SVLT ( $\beta=-0.299$ ,  $p=0.048$ ) remained significant on multiple regression analysis. In contrast, delayed recall ( $\beta=-0.256$ ,  $p=0.073$ ) and recognition on SVLT ( $\beta=-0.105$ ,  $p=0.510$ ), and COWAT supermarket ( $\beta=-0.165$ ,  $p=0.285$ ) were not found to be significantly different between the LE and HE groups.

### The neuroimaging findings depending on the education group

The degree of MTA was not different between the two groups. Only the tendency for milder MTA on the right side was observed in the LE group ( $p=0.058$ ) (Table 3). The ischemic burden encompassing white matter degeneration in both periventricular and deep white matter was similar according to the educational level.

## DISCUSSION

During our trial to identify the education effect on the clinical characteristics of mild AD, we found that the patients with LE had a more depressive mood. But, they were rather less impaired from their corresponding norm on K-MMSE and a few specified neuropsychological tests, copy time on RCFT ( $\beta=-0.437$ ,  $p=0.005$ ), and immediate recall on RCFT ( $\beta=-0.502$ ,  $p=0.001$ ) and SVLT ( $\beta=-0.299$ ,  $p=0.048$ ) compared with the highly educated patients.

Accumulating evidence suggests that better education is preventive against the development of dementia.<sup>2,3</sup> However,

after the onset of dementia, more studies suggest that the progress is faster in more educated individuals.<sup>13,14</sup> In accordance with this finding, the results of cortical thickness analysis demonstrated more severe cortical atrophy in AD dementia subjects with HE.<sup>15</sup> The cognitive reserve thanks to high education would be protective against the beginning of overt clinical symptoms of cognitive decline and impairment of daily activities.<sup>13,14</sup> It may delay the development of dementia although the brain pathology has progressed substantially.<sup>2,3</sup> However, in the present study, the two extreme educational groups did not show a significant difference in the severity of brain pathology in terms of MTA and vascular burden. We cannot exclude the possibility of missing meaningful results due to the fact that we did not perform delicate quantitative measurements. Interestingly, the negative deviations from the corresponding norm in neuropsychological tests were more profound in the HE group. Considering that the stage of dementia judged by CDR-SOB was comparable between the two groups, the lower z-score in the HE group suggests that these patients were more resistant to clinical onset of dementia despite the significantly declined cognitive performance from their premorbid state. Taken together, we can conclude that higher education is beneficial for prevention of the progression of dementia in the mild stage of AD. It is partly in contrast to the prior study which showed that the protective effect of high education did not persist after the late-stage of mild cognitive impairments.<sup>16</sup> Therefore, a subsequent study is necessary which incorporates the longitudinal data on this issue.

In the current study, the female gender was significantly more common in the LE group. The subjects in this study were older than 70 years. In their young days, Confucianism was still the dominant social ideology which opposed the women's right to take formal education. This might be the main reason for the much higher proportion of illiteracy in females. To exclude the confounding effect of the demographic dissimilarity between the two groups, we performed a multivariate analysis considering the confounders including gender. Among the significant variables on univariate analysis, depression, z-score on K-MMSE, copy time on RCFT, and immediate recall on RCFT and SVLT remained significant depending on the education group. Delayed recall which is the most distinct cognitive deficit in the early stage of late-onset AD lost its significance on regression analysis.

Our observation of more frequent depression in the LE group is consistent with the recent description in our country, which demonstrated a higher risk of depression in the community-dwelling elderly illiterate individuals.<sup>17</sup> Depressive mood could have a negative impact on the neuropsychological performance. However, this finding was not observed in

this study. The LE group was better at the cognitive tests after adjusting for gender, age, and education by using the z-score. Also, there was no correlation between the z-scores on the individual test and the extent of depression on GDSs.

In summary, we found that depressive mood was more prevalent in the LE group with illiteracy. However, diminution in a specified neuropsychological performance, copy time on RCFT, and immediate recall on RCFT and SVLT was milder than that in the HE group. A consideration of these clinical characteristics would be beneficial in treating illiterate individuals with mild AD.

### Conflicts of Interest

The authors have no financial conflicts of interest.

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