Geriatrics & Gerontology INTERNATIONAL Medline Indexed

Geriatr Gerontol Int 2015; **15:** *428–434*

ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Impact of cognitive reserve on the progression of mild cognitive impairment to Alzheimer's disease in Japan

Akira Osone, Reiko Arai, Rina Hakamada and Kazutaka Shimoda

Department of Psychiatry and Center for Dementia-Related Diseases, Dokkyo Medical University School of Medicine, Tochigi, Shimotsuga, Japan

Aim: The present study aimed to investigate whether cognitive reserve (CR), referring here to education and premorbid intelligence (IQ), is associated with the risk for progression from mild cognitive impairment (MCI) to Alzheimer's disease (AD).

Methods: A total of 51 patients with MCI and 59 patients with AD were prospectively enrolled for assessment with the Mini-Mental State Examination, the Japanese version of the cognitive subscale of the Alzheimer's Disease Assessment Scale, the Japanese version of the Nelson Adult Reading Test (JART), magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT), adjusting for sex, age at diagnosis, age at onset and duration of illness.

Results: SPECT findings showed hypoperfusion in the posterior cingulate gyri and precunei, suggesting that the participants were in the early or mild stage of AD or MCI. Voxel-based morphometry MRI showed no statistical differences between the two groups in gray matter loss in the entorhinal and hippocampal areas; however, multiple logistic regression analysis showed a significant difference in premorbid IQ measured with JART.

Conclusion: Despite the limitations of the cross-sectional design, the findings suggest that premorbid intellectual function might explain the discrepancy in clinical status between MCI and AD patients with a similar magnitude of brain pathology and comorbid medical disorders. **Geriatr Gerontol Int 2015; 15: 428–434.**

Keywords: Alzheimer's disease, cognitive reserve, education, mild cognitive impairment, premorbid IQ.

Introduction

Alzheimer's disease (AD) is the most common cause of dementia in elderly people. However, the relevance and independent contribution of risk factors, and of possible early signs, such as mild cognitive impairment (MCI) on the progression of AD, have not been investigated. Many studies have shown a strong association between a lower level of education, and higher prevalence and incidence of AD.[1,2] Higher education has also been reported to slow down cognitive and functional decline.[3] The concept of cognitive reserve (CR) suggests that brain pathology and age-related changes can be protected as a result of the way in which tasks are processed.[4] Although there is a wide range of putative indices of CR, the main indicator is thought to be premorbid intelligence (IQ).[5] However, its effect on the subsequent course of MCI to AD is less clear. Neuroimaging studies have begun to identify the neural substrate of CR, and numerous structural magnetic resonance imaging (MRI) studies have shown that atrophy of the medial temporal lobe, including the hippocampus and entorhinal cortex, is a sensitive marker of early AD.[6,7] However, the interaction between neuropsychological performance, brain pathology and CR has yet to be established.

The aim of the present study, therefore, was to investigate the relationship between neuropsychological performance, brain pathology and CR, including associated medical diseases.

Accepted for publication 4 March 2014.

Correspondence: Dr Akira Osone MD PhD, Department of Psychiatry, Dokkyo Medical University School of Medicine, 880 Kitakobayashi, Mibu, Tochigi 321-0293, Japan. Email: osone@dokkyomed.ac.jp

 doi: 10.1111/ggi.12292

Methods

The present study was approved by the ethics committee of Dokkyo Medical University School of Medicine. Patients were referred to our Center for Dementia-Related Diseases by their physician (40%) or were self-referred (60%). Study participants were 110 patients (41 men and 69 women; mean age [SD] 78.5 years [5.6 years] across all patients, 77.8 years [5.1 years) for men and 79.0 years [5.9 years] for women). All MCI and AD patients were Japanese, were enrolled consecutively, were informed about the purpose and procedures of the study, and signed an informed consent form before their participation in the study. Patients received a standardized clinical evaluation consisting of a physical examination, laboratory tests, and cognitive and functional assessments at the initial visit. Patients who took benzodiazepines, antidepressants or choline esterase inhibitors were excluded. Diagnoses were made at a clinical consensus meeting using relevant diagnostic guidelines, such as the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria,[8] for the diagnosis of AD and criteria outlined in Petersen *et al.*[9] or a 0.5 Clinical Dementia Rating (CDR)[10] for MCI. All the MCI patients were diagnosed with amnestic single-domain MCI.[11] Subjective and objective (corroborated by an informant) anamnestic evidence of progressive cognitive impairment were also required. In addition, hypoperfusion in the posterior cingulate cortex and precuneus were examined by single-photon emission computed tomography (SPECT) in MCI and AD patients, because the presence of hypoperfusion in parietal association areas and at the MCI stage have been reported to predict a rapid conversion to AD.[12] The patients were also asked to complete the Geriatric Depression Scale (short version), translated and localized for Japanese speakers.[13] Patients with major depressive or other severe psychiatric disorders were excluded.

The National Adult Reading Test (NART),[14,15] is widely used to measure premorbid IQ of English-speaking patients with dementia. Previous studies have also been carried out to examine the relationship between premorbid IQ and progression of AD[2] or functional outcome in AD[16] measured using the American version of the Nelson Adult Reading Test or NART. We used the Japanese version of the NART (JART), which has been proven to show good validity for measuring premorbid IQ and to be independent of present cognitive function in AD patients in Japan,[17] and the Mini-Mental State Examination (MMSE) scale,[18] a widely used index of cognitive status that has been validated for use with Japanese subjects.[19]

The cognitive subscale of the Alzheimer's Disease Assessment Scale is the most widely used tool in clinical trials of AD.[20] For the Japanese version of the Alzheimer's Disease Assessment Scale (ADAS-J cog), mean scores (SD) were 12.8 (3.7) for MCI (CDR = 0.5), 21.2 (7.4) for mild AD (CDR = 1), 29.0 (11.7) for moderate AD (CDR = 2) and 42.1 (10.8) for severe AD (CDR = 3), and the test showed high sensitivity (98.1%) and specificity (95.1%).[21] In the present study, the ADAS-J cog was administered by two skilled clinical psychologists (R A and R H).

MRI procedures

MRI was carried out using a 1.5-T system (Magnetom Symphony Quantum or Sonata; Siemens, Erlangen, Germany). For diagnosis, magnetization-prepared rapid gradient echo of sagittal 3-D sequence images (repetition time [TR] 1700 ms; echo time [TE] 3.93 ms; 4-mm thickness; 15° flip angle; 230-mm field of view; inversion time [TI], 1800 ms; 256×256 matrix; $176 \times$ 1.25-mm contiguous sections; gapless) and axial T2-weighted turbo spin echo (TSE) images (TR 3800 ms; TE 99.0 ms; 6-mm thickness; 1.5-mm slice-gap) were obtained for diagnosis. Coronal TSE imaging (TR 9000 ms; TE 107 ms; 4-mm thickness; 1-mm slice-gap) was also carried out for voxel-based morphometry (VBM) analysis. The acquired MR images were reformatted to gapless 4-mm thickness trans-axial images for analysis with Statistical Parametric Mapping 2002 (SPM2; Wellcome Department of Imaging Neuroscience, London, UK) running on MATLAB (The MathWorks, Sherborn, MA, USA). We used a software program running on Windows XP and Vista called the voxel-based specific region analysis system for Alzheimer's disease (VSRAD plus; Eisai, Tokyo, Japan),[22] which automatically analyzes 3-D T1-weighted MRI data as a series of segmentation, anatomical standardization and smoothing using SPM2, and that has high discrimination accuracy of 87.8%.[23] The *Z*-score of VSRAD, defined as (normal mean – patient value) / (normal SD), representing the magnitude of gray matter density discrepancy, $n \times$ SD, was used as an indicator of the degree of atrophy of the entorhinal cortex and hippocampus. The *Z*-score maps were displayed by overlay on tomographic sections.

Statistical analysis

Group differences in demographic variables were evaluated using independent sample *t*-tests for continuous data, and with the odds ratio (OR) and 95% confidence interval (CI) for categorical data. Pearson's correlation coefficient was calculated to examine the relationship between years of education and premorbid IQ, and multiple regression analysis was carried out to explore the relationship between MCI and AD scores. Analyses were carried out using the SPSS version 20 statistical

Table 1 Demographic characteristics and other variables of patients with mild cognitive impairment or Alzheimer disease

	MCI (n = 51)	AD (n = 59)	P
Sex (male/female)	19/32	22/37	1.00 (0.46–2.17)
Age at diagnosis (years)	77.7 (5.0)	79.3 (6.0)	0.14
Age at onset (years)	76.0 (5.0)	77.1 (7.4)	0.69
Duration of illness (months)	18.6 (6.0)	20.0 (19.3)	0.69
Education (years)	11.4 (2.6)	10.2 (2.8)	0.03
<12	25 (49.0%)	21 (35.6%)	0.57 (0.27–1.23)
12–16	18 (35.3%)	33 (55.9%)	2.32 (1.08–5.03)
≥16	8 (15.7%)	5 (8.5%)	0.50 (0.15–1.63)
MMSE score	24.3 (2.9)	18.7 (3.2)	0.00
ADAS-J cog score	10.1 (4.6)	18.3 (6.9)	0.00
JART score	100.8 (12.8)	91.2 (13.1)	0.00
Hypertension	31 (60.8%)	27 (45.8%)	0.54 (0.25–1.16)
Diabetes mellitus	8 (15.7%)	9 (15.3%)	1.00 (0.34–2.73)
Hyperlipidemia	16 (31.4%)	10 (16.9%)	0.45 (0.18–1.10)
VSRAD Z-score	2.49 (1.31)	2.96 (1.20)	0.06
0–1	5 (9.8%)	4 (6.8%)	0.67 (0.17–2.64)
1–2	17 (33.3%)	9 (15.3%)	0.36 (0.14–0.90)
2–3	17 (33.3%)	22 (37.3%)	1.19 (0.54–2.61)
>3	12 (23.5%)	24 (40.7%)	2.22 (0.97–5.11)

Data presented as mean (SD) or n (%). P-values were calculated using the t-test or were odds ratios (95% confidence interval). ADAS-J cog, Cognitive subscale of the Japanese version of the Alzheimer's Disease Assessment Scale; JART, Japanese Adult Reading Test; MMSE, Mini-Mental State Examination; VSRAD, voxel-based specific region analysis system for Alzheimer's disease software program, where Z-scores show the degree of gray matter loss in the entorhinal and hippocampal areas (clinical criteria are: 0–1, normal; 1–2, slight; 2–3, moderate; >3, severe)

software package for Mac (IBM, Armonk, NY, USA). An alpha level of 0.05 was considered statistically significant.

Results

Table 1 summarizes patient demographic data and Table 2 shows sex differences in the 110 patients in the present study. There were no significant differences in sex, mean age at onset, mean onset of illness or mean duration of illness between the MCI and AD groups, or between men and women in general. However, statistical differences were found in MMSE score (t = 8.95, df = 108, P = 0.00) and ADAS-J cog score (t = 5.65, df = 108, P = 0.00) between the MCI and AD groups, showing that MCI patients had better cognitive performance than AD patients. In terms of education, MCI patients had more years of education (t = 2.26, df = 108, P = 0.03). All the patients in the AD group showed late-onset mild AD, where NART is a valid estimator of premorbid ability.[24] JART-predicted IQ was higher in MCI patients than in AD patients (t = 3.85, df = 108, P = 0.00).

There were no statistical differences between the MCI and AD groups in terms of lifestyle-related diseases, such as hypertension, diabetes mellitus and hyperlipidemia. VSRAD Z-score for MCI (mean 2.49) was lower than that for AD (mean 2.96), suggesting a tendency for less atrophy compared with AD patients. However, Z-score and degree of atrophy did not differ significantly between the MCI (mean 2.49, SD 1.31) and AD (mean 2.96, SD 1.20) groups, suggesting a similar magnitude of severity, namely, moderate atrophy. The only differences between the MCI and AD patients other than the diagnostic variables were years of education (P = 0.03) and JART-predicted IQ score (P = 0.00).

Figure 1 shows the relationship between VSRAD Z-score and ADAS-J cog score divided by a premorbid IQ of 100. Pearson's correlation coefficient was 0.42 for the patients with low premorbid IQ (<100), suggesting a weak correlation between VSRAD Z-score and ADAS-J

Table 2 Sex differences for the total 110 patients with either mild cognitive impairment or Alzheimer disease

	Men (n = 41)	Women (n = 69)	P
MCI/AD	019/22	32/37	0.99 (0.46–2.17)
Age at diagnosis (years)	78.5 (5.6)	79.0 (5.9)	0.19
Age at onset (years)	76.6 (6.4)	77.1 (6.9)	0.27
Duration of illness (months)	22.0 (21.4)	17.4 (14.8)	0.23
Education (years)	11.8 (3.1)	10.1 (2.3)	0.00
<12	22 (53.7%)	24 (34.8%)	2.17 (0.99–4.78)
12–16	9 (35.3%)	42 (60.9%)	5.53 (2.29–13.38)
>16	10 (24.4%)	3 (4.3%)	7.10 (1.82–27.62)
MMSE score	21.2 (3.7)	21.3 (4.3)	0.89
ADAS-J cog score	13.3 (6.2)	12.9 (7.2)	0.80
JART score	97.7 (13.6)	94.5 (13.9)	0.25
Hypertension	22 (53.7%)	36 (52.2%)	1.06 (0.49–2.30)
Diabetes mellitus	8 (19.5%)	9 (13.0%)	1.62 (0.57–4.59)
Hyperlipidemia	8 (19.5%)	18 (26.1%)	0.69 (0.27–1.76)
VSRAD Z-score	2.68 (1.24)	2.77 (1.31)	0.74
0–1	3 (7.3%)	6 (8.7%)	0.83 (0.20–3.51)
1–2	10 (24.4%)	16 (23.3%)	1.07 (0.43–2.64)
2–3	16 (39.0%)	23 (33.3%)	1.28 (0.57–2.86)
>3	12 (29.3%)	24 (34.8%)	0.78 (0.34–1.79)

Data presented as mean (SD) or n (%). P-values were calculated using the t-test or were odds ratios (95% confidence interval). AD, Alzheimer's disease; ADAS-J cog, Cognitive subscale of the Japanese version of the Alzheimer's Disease Assessment Scale; JART, Japanese Adult Reading Test; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; VSRAD, voxel-based specific region analysis system for Alzheimer's disease software program, where Z-scores show the degree of gray matter loss in the entorhinal and hippocampal areas (clinical criteria are: 0–1, normal; 1–2, slight; 2–3, moderate; >3, severe)

cog score. However, Pearson's correlation coefficient was 0.01 for the patients with high premorbid IQ (≥100).

Figure 2 shows the relationship between years of education and premorbid IQ measured with JART. Pearson's correlation coefficient was 0.41 for the total 110 patients, suggesting a weak correlation between years of education and premorbid IQ. However, a sex difference was observed; Pearson's correlation coefficient for men (0.44) was higher than that for women (0.38).

Discussion

Many studies have examined the risk and protective factors that underlie AD pathology by neuroimaging or using biomarkers. In particular, considerable efforts have been made to identify patients with early-stage AD with the aim of initiating effective treatment at an early stage.[6] Studies have also reported a relationship between premorbid IQ and cerebral glucose metabolism in patients with AD.[1] However, no studies have measured CR, namely, the ability to cope with this pathology.[4]

Although we used JART to assess premorbid intellectual function, the test has some limitations. For example, as pointed out by Matsuoka *et al.*, JART-predicted IQ scores have a smaller range (75.9–124.1) than the original NART (68.6–130.6).[17] As a result, the JART-predicted IQ scores for participants with very high intelligence will be underestimated, whereas those of participants with very low intelligence will be overestimated. In addition, there are many definitions of IQ, and JART might reflect only one aspect of IQ, especially literacy.

As shown in Figure 1, for patients with low premorbid IQ (<100), the more severe the degree of entorhinal and hippocampal atrophy, the worse the cognitive performance, suggesting a lower protective effect by CR. In patients with high premorbid IQ (≥100), however, CR might compensate for increasing entorhinal and hippocampal atrophy.

As shown in Figure 2, unlike premorbid IQ, years of education typically had limited variance, especially among women,[16] and women in Japan had less opportunity to receive education than men before the end of

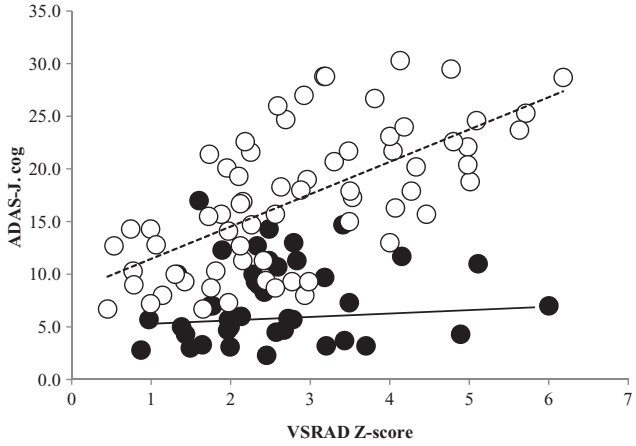

Figure 1 Correlation between voxel-based specific region analysis system for Alzheimer's disease (VSRAD) Z-score and the Japanese version of the Alzheimer's Disease Assessment Scale (ADAS-J cog) score. The patients were divided into two groups according to premorbid intelligence (IQ) measured with the Japanese version of the Nelson Adult Reading Test (<100 or ≥100). Pearson's *r* was 0.42 (dashed line) for patients with low premorbid IQ (<100), suggesting a weak positive correlation. The correlation coefficient for patients with high premorbid IQ (≥100) was much lower (Pearson's *r* = 0.01, solid line) than that for patients with low premorbid IQ, suggesting a protective effect by cognitive reserve. VSRAD, a voxel-based specific region analysis system for Alzheimer's disease software program, where Z-scores show the degree of gray matter loss in the entorhinal and hippocampal areas (clinical criteria are: 0–1, normal; 1–2, slight; 2–3, moderate; >3, severe).

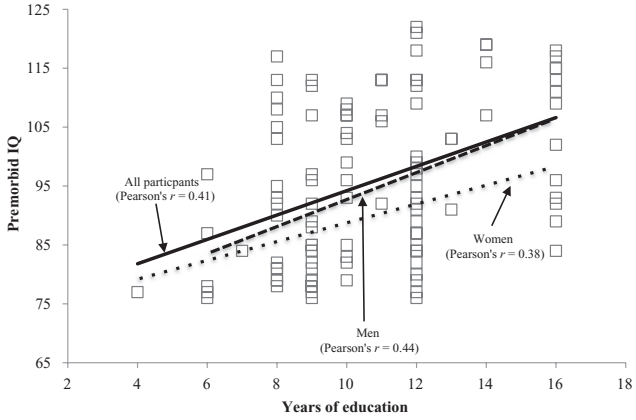

Figure 2 Correlation between years of education and premorbid intelligence (IQ) measured using the Japanese version of the Nelson Adult Reading Test. Note that Pearson's *r* was 0.41 for the total 110 patients, suggesting a weak correlation, whereas the correlation for men (*r* = 0.44) was higher than that for women (*r* = 0.38), suggesting a sex difference.

World War II. Such unfavorable socioeconomic circumstances might, therefore, have limited an individual's opportunities to receive appropriate education. There was no statistical significance ($t = 1.23$, df = 108, $P = 0.29$) in age at diagnosis between the 41 men (mean 77.5 years, SD 5.1 years) and 69 women (mean 79.0 years, SD 5.9 years) participating in the present study. Although men received more years of education (mean 11.8 years, SD 3.1 years) than women (mean 10.1 years, SD 2.3 years; $t = 3.00$, df = 108, $P = 0.004$), there was no statistical significance ($t = 1.17$, df = 108, $P = 0.25$) in premorbid IQ between men (mean 97.7, SD 13.6) and women (mean 94.5, SD 13.9). These results suggest that years of education is not a determinant factor of premorbid IQ. The effect of the education level on the risk for AD is controversial, with a recent review reporting that more years of education did not uniformly attenuate the risk for dementia, consistent with the present findings.[25]

Analyses of comorbid medical conditions in AD patients have suggested a strong association between medical comorbidity and cognitive status in AD patients.[26] Furthermore, a prospective cohort study showed that coexisting medical conditions could have some effect on the progression of AD.[27] Furthermore, lifestyle-related diseases, such as hypertension, diabetes mellitus and hyperlipidemia, are associated with a risk of AD.[28–30] Although the comorbid rate seemed to be higher in MCI patients in the present study, there was no statistical difference between the MCI and AD groups, suggesting that there is no association with the progression of MCI to AD. However, further longitudinal studies are still required.

In the 1990s, anatomical studies suggested that atrophic progression from the transentorhinal region to entorhinal and transentorhinal regions was correlated with a gradual worsening of clinical symptoms.[31] However, it is difficult to evaluate atrophy of the entorhinal cortex by visual inspection alone. Accordingly, numerous MRI studies have since shown that atrophy of the medial temporal lobe, including the hippocampus as well as the entorhinal cortex, is indeed associated with the onset of symptoms of early AD.[6,7,32] This was shown to be especially true with the earliest pathological change, which occurs in the entorhinal cortex. Z-score images obtained with VBM are a powerful diagnostic tool for detecting mild AD.[33] That is, the purpose of neuroimaging in AD is not for diagnosis of advanced AD, but rather for very early AD in the form of conversion from MCI to AD. This finding might be related to anatomical findings showing that the regions are linked through the circuit of Papez to not only emotions, but also memory function.[22] However, brain reserve,[34] such as that indicated by anatomical or neuroimaging results, does not directly reflect individual memory function, as shown in the present study. In contrast, CR suggests that the brain actively attempts to cope with brain damage by using preexisting cognitive processes or by enlisting compensatory processes.[35]

With sex, age at onset, duration of illness, years of education, magnitude of atrophy of entorhinal and hippocampal areas, and three coexisting lifestyle-related diseases as independent variables, and MCI and AD as dependent variables, multiple logistic regression analysis showed that the only difference between the MCI and AD groups was in premorbid IQ ($P = 0.00$, OR 1.06, 95% CI 1.02–1.09, partial regression coefficient 0.05), and that years of education had no statistical significance. This suggests that premorbid IQ represents a more robust CR than education, with a seemingly protective effect on the progression of MCI to AD through increased CR.

The concept of CR arose from observations that there appears to be no direct relationship between the magnitude of brain pathology and clinical manifestation.[35] It has been hypothesized that CR modifies the relationship between pathology and clinical symptoms, and the present results suggest that the main factor affecting CR is premorbid IQ. Consideration of CR could, therefore, improve our understanding of individual differences in the progression of AD. Further longitudinal studies of, for example, occupational exposure and leisure activities are now required to clarify the main factors involved in the progression of cognitive decline.

Acknowledgment

We thank all patients and staff who took part in this study.

Disclosure statement

The authors declare no conflicts of interest.

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