ORIGINAL ARTICLE

Effects of aging on behavioral symptoms in Alzheimer's disease

Kimiko KONISHI,[1,2] Koji HORI,[1,2] Tatsuro ODA,[3] Itaru TOMINAGA,[4] Toshiyasu ASAOKA,[4] Mitsugu HACHISU[5] and Toshiaki SHIBASAKI[2]

[1]Department of Psychiatry, Showa University Northern Yokohama Hospital, Kanagawa, [2]Department of Pharmatherapy, School of Pharmaceutical Sciences, Keiogizyuku University, Tokyo, [3]Department of Psychiatry, Takasukouen Mental Clinic, Chiba, [4]Department of Psychiatry, National Shimofusa Hospital, Chiba, and [5]Department of Clinical Psychopharmacy, School of Pharmaceutical Sciences, Showa University, Tokyo, Japan

Correspondence: Dr Koji Hori MD PhD, Department of Psychiatry, Showa University Northern Yokohama Hospital, 35-1 Chigasakichuo, Tsuzuki-ku, Yokohama, Kanagawa 224-8503, Japan.
Email: kojihori@showa-university-fujigaoka.gr.jp

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Abstract

Aim: The aim of the present study was to evaluate the relationship between aging and the behavioral and psychological symptoms of dementia (BPSD) in patients with Alzheimer's disease (AD).

Methods: Eligible subjects were consecutively referred AD patients with BPSD. According to patient age at the time of the test, the AD patient group ($n = 79$, whole AD group (WADG)) was divided into two groups: a relative older group (OG) in the whole AD group (WAD) (age at the time of test was 81 years or more, $n = 40$) and a relative younger group (YG) in the WAD (age at the time of test was below 81 years, $n = 39$). A comparison was made of the demographic data (sex difference, educational level and severity of dementia), cognitive functions and BPSD between the groups. BPSD was evaluated using the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD). The factor analysis of BPSD was conducted in the WADG as well as in the OG and YG.

Results: Sex difference, educational level, severity of dementia and cognitive functions were not different; however, the total score of the BEHAVE-AD symptom domain in diurnal rhythm was significantly higher in the OG than in the YG (Student's *t*-test: $P < 0.05$). Factor analysis showed that psychosis was the first factor in the OG, but was the third factor in the YG and that the psychotic symptoms were caused by anxieties and phobias in the OG.

Conclusion: From these results, we found that the effects of aging on the BPSD in AD were characterized by diurnal rhythm disturbance and psychosis.

INTRODUCTION

In many countries, including Japan, life expectancy is increasing.[1] As a result, the eldest of the aged population are increasing in number. Because aging is one of the main risk factors for dementia,[2] the number of patients with dementia is increasing, especially in the eldest of the aged.[3] Aging also has effects on cognitive functions and neuropsychiatric symptoms. After all, the symptoms of dementia in the eldest of the aged are affected not only by the disease, but also by aging and the clinical features of dementia in the eldest of the aged may be different from those in the younger aged population. In view of neuropathology, there are different findings regarding the eldest of the aged populations than in the younger aged.[4–6] Prohovnik *et al.* reported that in the eldest aged patients with Alzheimer's disease (AD) senile plaques and neurofibrillary tangles were not necessarily correlated with cholinergic deficit.[7] Many authors have compared clinical symptoms in the eldest of the aged with and without dementia (85 years and over, 90 years and over, and 100 years and over) with those in the younger aged.[8–16] In view of neuropsychiatric symptoms, the frequency and severity of behavioral and psychological symptoms of dementia (BPSD) were compared in the eldest of the aged with AD and the younger aged populations with AD. However, there is a limited number of reports regarding the qualitative

differences of neuropsychiatric symptoms between the eldest of the aged and the younger aged, although neuropsychiatric symptoms are important because of the effect they have on the burden of caregivers and early institutionalization.[17–20] Therefore, in the present study we compared not only the severity of BPSD in patients in the relative older AD group but also the factor structures of BPSD between both groups. We then investigated which symptoms domains were mainly affected by aging and how aging affected BPSD in AD.

METHODS

Eligible subjects for the study were patients with probable AD who were referred consecutively to the psychogeriatric clinic of National Shimofusa Hospital because of BPSD between 1 March 2000 and 31 March 2005. All patients were diagnosed by the criteria developed by the working group of the National Institute of Neurological and Communicative Disorders and Stroke in collaboration with the Alzheimer's Disease and Related Disorders Association.[21] To avoid confounding factors, confounding effects of non-AD related and non-aging factors (physical illnesses, psychological factors and environmental factors), we excluded patients with other psychiatric diagnoses prior to the onset of dementia, including drug and alcohol dependency, and/or prominent history of cerebral hemorrhage or infarction. To ensure that patients did not suffer from drug toxicity symptoms and delirium, and that BPSD were not due to physical illness, we excluded patients whose symptoms occurred after medication had been changed, with abrupt onset of BPSD or with an active physical illness. We only included patients with medical illnesses that were controlled with treatment. Patients were required to be ambulatory or ambulatory with a walker. We also included patients who had adapted to daily life with the help of caregivers until BPSD appeared. A total of 159 subjects were enrolled according to the above criteria.

BPSD fluctuate over time and may also be absent for long periods before returning.[20,22] Therefore, we only selected patients who showed first BPSD, whose BPSD had not changed, and who were referred to our clinic within a year after BPSD had appeared. These procedures reduced the number of eligible subjects to 79 (whole AD group (WADG)).

We evaluated demographic data (sex difference, educational level, age at onset of dementia, age at the time of test and severity of dementia), cognitive function and BPSD at study entry. The severity of dementia was evaluated using Functional Assessment Staging (FAST).[23] Cognitive function was evaluated using the Mini-Mental State Examination (MMSE),[24] and BPSD were assessed by the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD),[25] which measures behavioral and psychological symptoms in seven symptom domains (paranoid and delusional ideation, hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbance, and anxieties and phobias). BEHAVE-AD is scored on a four-point scale according to disease severity. We used the total score for each symptom domain (diurnal rhythm disturbances is treated as a single item).

First, according to the age at the time of the test, AD patients were divided into two groups: a relative older group in the WAD (age at the time of test was 81 years and over, $n = 40$, OG) and a relative younger group in the WAD (age at the time of test was below 81 years, $n = 39$, YG). Because the median value of age at the time of the test in our study patients was 81, the numbers of the two groups were almost the same.

Second, we compared the demographic data, cognitive function and each symptom domain of the BEHAVE-AD between the two groups. Sex differences were compared between the OG and YG with χ^2 test of Yates' correction. The other demographic data, cognitive function and BPSD were compared between the two groups using Student's *t*-test. $P < 0.05$ was accepted as statistically significant.

Third, we performed a factor analysis on BEHAVE-AD items followed by an orthogonal rotational procedure (varimax rotation) to extract meaningful descriptions of BPSD in the OG and YG. Factors were selected on the basis of eigenvalues greater than 0.1. The factor consists of the items those factor loadings were 0.45 and higher were included as there had been an interrelationship with each other.

Data were analyzed using statistical software package SSPS-J (Statview Inc, Tokyo, Japan).

Informed consent was obtained from proxies of patients (mainly the husband, wife, children or siblings) and, if possible, from the patients themselves.

The study was approved by the Ethical Committee of National Shimofusa Hospital.

RESULTS

Table 1 shows the mean values of the demographic data and MMSE scores in the OG and YG. Table 2 shows each domain of BEHAVE-AD in the OG and YG. Sex difference, educational level, severity of dementia and cognitive function were not significantly different between the OG and YG. We evaluated that the activity of dairy living (ADL) were not significantly different between the OG and YG because FAST scores were not significantly different between the OG and YG. The scores of the BEHAVE-AD subdomain of diurnal rhythm disturbances in the OG group were significantly higher than in the YG group ($P < 0.05$).

By factor analysis with criterion on the basis of eigenvalues greater than 0.1, three factors in BEHAVE-AD in the OG and YG were reduced. The results of factor analysis of BPSD using BEHAVE-AD are shown in Table 3A (in the OG) and Table 3B (in the YG). In both groups, three meaningful factors were extracted and these three factors represented clinically interpretable domains. In the YG group, these factors explained 79.1% of the variance. Factor 1 represented 'disrupted behaviors' (explained variance: 33.8%) – activity disturbances, aggressiveness, and diurnal rhythm disturbances. Factor 2 represented 'depression' (explained variance: 29.7%) – affective disturbances, and anxieties and phobias. Factor 3 represented 'psychosis' (explained variance: 15.6%) – paranoid and delusional ideation, and hallu-

Table 1 Demographic data in the OG and YG

	OG	YG	*P*-value
Number (male/female)	40 (17/23)	39 (18/21)	0.9178
Educational level (years)	8.65 (3.86)	9.97 (4.28)	0.1498
Age at dementia onset (years)	84.35 (3.85)	68.82 (6.59)	–
Test age (years)	87.05 (3.56)	72.46 (6.83)	–
FAST stage score	4.92 (1.02)	5.05 (1.12)	0.6025
MMSE	9.33 (6.36)	12.46 (8.85)	0.0739

$P < 0.05$ (Student's *t*-test). Data are given as mean (SD) except numbers. AD, Alzheimer's disease; OG, relative older group of Alzheimer's disease patients (age at the time of test was 81 years or more); YG, relative younger group of Alzheimer's disease patients (age at the time of test was less than 81 years); FAST, Functional Assessment Staging; MMSE, Mini-Mental State Examination. Comparisons of sex difference in the OG and in the YG were performed by χ^2 test with Yate's correction.

Table 2 Mean total score of each BEHAVE-AD symptom domain in the OG and YG

Item	OG	YG	*P*-value
Delusion	1.3 (2.0)	2.1 (2.4)	0.0937
Hallucination	0.9 (1.1)	1.0 (1.2)	0.7042
Activity disturbance	2.7 (2.2)	3.4 (2.7)	0.2270
Aggressiveness	1.8 (1.9)	2.3 (2.4)	0.2824
Rhythm disturbance	1.6 (0.8)*	0.9 (1.0)	0.0002
Affection	0.9 (1.0)	1.0 (1.3)	0.7027
Anxiety	1.3 (1.6)	1.4 (1.9)	0.7371

*$P < 0.05$ (Student's *t*-test). Data are given as mean (SD). AD, Alzheimer's disease; OG, relative older group of Alzheimer's disease patients (age at the time of test was 81 years or more); YG, relative younger group of Alzheimer's disease patients (age at the time of test was less than 81 years); BEHAVE-AD, Behavioral Pathology in Alzheimer's Disease Rating Scale: delusion, paranoid and delusional ideation; hallucination, hallucinations; activity disturbance, activity disturbances; aggressiveness, aggressiveness; rhythm disturbance, diurnal rhythm disturbances; affection, affective disturbances; anxiety, anxieties and phobias.

Table 3 (A) Results of the varimax rotation of factor analysis on BEHAVE-AD scale in the OG. (B) Results of the varimax rotation of factor analysis on BEHAVE-AD scale in the YG

	Factor (A)			Factor (B)		
	1	2	3	1	2	3
% Variance	Psychosis 30.0%	Disrupted behaviors 24.4%	Agitated depression 17.0%	Disrupted behaviors 33.8%	Depression 29.7%	Psychosis 15.6%
Delusion	0.821	–0.073	0.231	0.059	–0.083	0.857
Hallucination	0.892	0.159	–0.073	0.149	0.228	0.867
Activity disturbance	0.024	0.750	0.024	0.776	–0.288	–0.317
Aggressiveness	0.141	0.468	0.758	0.884	–0.039	0.227
Rhythm disturbance	0.059	0.721	0.057	0.752	0.029	0.435
Affection	0.073	–0.191	0.922	–0.055	0.920	0.082
Anxiety	0.493	–0.572	0.276	–0.122	0.903	0.025

AD, Alzheimer's disease; OG, relative older group of Alzheimer's disease patients (age the time of test was 81 years or more); YG, relative younger group of Alzheimer's disease patients (age the time of test was less than 81 years); BEHAVE-AD, Behavioral Pathology in Alzheimer's Disease Rating Scale: delusion, paranoid and delusional ideation; hallucination, hallucinations; activity disturbance, activity disturbances; aggressiveness, aggressiveness; rhythm disturbance, diurnal rhythm disturbances; affection, affective disturbances; anxiety, anxieties and phobias; ▒ symptom with a factor loading ≥0.450.

cinations. On the contrary, in the OG, three meaningful factors were also extracted. These factors were, however, different from those in the YG. These three factors explained 71.4% of the variance. Factor 1 represented 'psychosis' (explained variance: 30.0%) – paranoid and delusional ideation, hallucinations, and anxieties and phobias. Factor 2 represented 'disrupted behaviors' (explained variance: 24.4%) – activity disturbances, aggressiveness, and diurnal rhythm disturbances. Factor 3 represented 'agitated depression' (explained variance: 17.0%) – aggressiveness and affective disturbances.

DISCUSSION

In the patients with probable AD, the differences of BPSD between the OG and YG were related to aging because we excluded patients whose symptoms occurred after medication had been changed, with abrupt onset of BPSD or with an active physical illness at study entry and we only included patients whose medical illness was controlled with treatment. Moreover, enrolled patients were required to be ambulatory or ambulatory with a walker and we included patients who had adapted to daily life with the help of caregivers until BPSD appeared. We also evaluated that ADL were not significantly different between the OG and YG because FAST scores were not significantly different between the OG and YG. In view of subjective factors, sex difference, educational level, severity of dementia and cognitive function were similar in both the YG and OG. In the present study, we could contribute the aging effect on BPSD in AD. These differences are more prominent in the eldest of the aged patients with dementia (85 years and over or 90 years and over) and have been described in previous studies.[13–16]

First, in the OG, the total score of the BEHAVE-AD symptom domain of diurnal rhythm disturbances was significantly higher than in the YG (Student's *t*-test, $P < 0.05$). This meant that diurnal rhythm disturbance was the most severe symptom in the OG. This finding is compatible with those of our previous reports showing that 'wakes up at night for no obvious reason' and 'wanders in the house at night' were more frequent in AD patients whose BPSD appeared after 90 years of age than in AD patients whose BPSD appeared before 90 years of age.[14] Because delirium was considered to be related to increasing age,[26] the fact that diurnal rhythm disturbance was related to increasing age might be attributed to the propensities of delirium in the eldest of aged patients.

Second, although both in the YG and OG three factors were extracted, the basic structures of BPSD in the OG were different from those in the YG. In the YG, Factor 1 represented 'disrupted behaviors'. Factor 2 represented 'depression'. Factor 3 represented 'psychosis'. This result was compatible with those of previous studies using another tool for evaluating BPSD in demented patients.[27–30] However, in the OG, Factor 1 represented 'psychosis', Factor 2 represented 'disrupted behaviors' and Factor 3 represented 'agitated depression'. 'Disrupted behaviors' was the first factor and explained 33.8% variance in the YG; however, it was the second factor and explained 24.4% variance in the OG. This did not mean that 'disrupted behaviors' was affected mainly by aging. Our result was compatible with those of previous reports showing that wandering was one of the most frequent symptoms in AD[19,20,22] because it was included in 'disrupted behaviors'. On the contrary, 'psychosis' was the first factor and explained 30.0% variance in the OG; however, it was the third factor and only explained 15.6% variance in the YG, although the severity of psychosis was not significantly different between the OG and YG. This meant that 'psychosis' was the most prominent symptom in the OG and more prominent than in the YG, and also meant that 'psychosis' was affected mainly by aging as has been reported previously.[13,15,16] In particular, Hamuro *et al.* reported that hallucination and delusional misidentification were the most prominent symptoms in the eldest of the aged population with dementia.[16] Anxiety and phobia were connected to psychotic symptoms and aggressiveness. In addition, affective disturbance was also connected to aggressiveness, which caused agitated depression in the OG. Ostling and Skoog commented that frequency of psychotic symptoms might be higher in the non-dementia population-based samples of the eldest of the aged and that psychotic symptoms were associated with depression in these populations.[8] Our result indicated that in AD, psychosis and aggressiveness became related with depression and depression-related symptoms by the aging process. Alternatively, although the relationship between aging and depression is ambiguous,[31] at least, depression or depression-related symptoms in patients with AD are

affected by aging and are connected to psychotic symptoms or disrupted behaviors.

From these results, we considered that the effects of aging on clinical features of patients with dementia with AD were characterized by two symptoms: one was disturbance of the sleep–wake pattern; the other was psychosis. We also considered that these symptoms were affected not only by disease, but also by aging.

There are two clinical implications of our study. First, if patients with AD are referred who are relatively older, it might have better to utilize group therapies for these patients. The authors of a previous report have commented on the efficacy of group therapies for demented patients.[32] We also reported that group therapies are effective for ameliorating diurnal rhythm disturbances.[33] Second, if patients with AD are referred who are relatively older and show psychotic symptoms, it might be better to prescribe antidepressants instead of antipsychotics because it is possible that depression or depression-related symptoms are connected to psychotic symptoms or disrupted behavior. Moreover, a warning on prescription of antipsychotic agents to elderly patients with dementia should be issued to increase mortality.[34]

There are several limitations in the present study: the sample size was small, there were no control subjects, and we did not observe cross-sectional and longitudinal courses of cognitive dysfunctions. Moreover, we only considered the factors related to patients. BPSD were caused not only by disease-related factors, but also by physical illnesses, psychological factors and environmental factors. Further investigations are required to delineate the relationship between cognitive dysfunctions and the features of BPSD in AD.

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