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■ Original Article

Risk Factors of Behavioral and Psychological Symptoms in Patients with Alzheimer Disease: The Clinical Research of Dementia of South Korea Study

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Background: Few studies have evaluated risk factors for behavioral and psychological symptoms of dementia at the initial assessment for Alzheimer disease in large patient samples. In this study, the factors influencing Alzheimer disease were examined using the Clinical Research of Dementia of South Korea data.
Methods: This cross-sectional study was conducted using data of 1,128 patients with Alzheimer disease. The behavioral and psychological symptoms of dementia were examined using the Korean version of the Neuropsychiatric Inventory. Demographic characteristics, health-related behavior, neuropsychological tests, comorbidities, blood test results, and caregiver characteristics were assessed. Median logistic regression analysis with adjustment for covariates was conducted.
Results: The behavioral and psychological symptoms of dementia were negatively associated with memory (P=0.022) and frontal/executive (P<0.001) function in the Seoul Neuropsychological Screening Battery-dementia, Barthel Index for Activities of Daily Living (P<0.001), Korean version of the Mini-Mental State Examination score (P=0.003), and caregiver age (P=0.005) after adjustment for confounding factors, and positively associated with the Seoul-Instrumental Activities of Daily Living score (P<0.001), Clinical Dementia Rating Sum of Box (P<0.001), Global Deterioration Scale score (P<0.001), abnormality of free T4 level (P<0.001), anemia (P<0.001), and family history of stroke (P=0.001). Patients with female caregivers exhibited more severe behavioral and psychological symptoms of dementia than those with male caregivers.
Conclusion: Behavioral and psychological symptoms of dementia in Alzheimer disease patients were associated with various risk factors including the inability to live independently and Alzheimer disease severity. These findings suggest that prevention and treatment strategies for the behavioral and psychological symptoms of dementia should be comprehensive.

Keywords: Behavioral Symptoms; Alzheimer Disease; Risk Factors; Clinical Research of Dementia of South Korea Study

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INTRODUCTION

Dementia is a neurodegenerative disease caused by gradual loss of cortical neurons, and characterized by a progressive deterioration in memory, other cognitive functions, self-care, and personality.[1] According to a Korean epidemiologic survey of dementia conducted in 2012, the prevalence rate of dementia among persons aged >65 years was 9.2%, and the number of persons with dementia was 540,755 (155,955 males and 384,800 females, which is expected to increase to 2,710,000 by 2050.[2]

The behavioral and psychological symptoms of dementia (BPSD) involve psychotic, affective, and behavioral elements. The symptoms, such as anxiety, agitation, nervousness, depression, elation, abnormal expression of feelings, emotional incontinence, delusion, or hallucination, can lead to rapid cognitive deterioration and functional impairment in patients, emotional and physical distress in family members and caregivers, and increased medical expenses.[3]

Alzheimer disease (AD) is the most common cause of dementia in Korea. The pathogenesis of BPSD in AD patients has not been clearly delineated; however, emerging literature suggests that neurochemical, neuropathological, (e.g., cholinergic system dysfunction[4]), and genetic factors all contribute.[5] Thus, categorization of BPSD in clusters accounting for their natural course, prognosis, and treatment response may be useful in clinical practice.

In addition to the influence of dementia stage and subtype, patient factors, including age, sex, psychotropic medication use, combined neuropsychiatric symptoms such as depression or lack of disease insight, neurocognitive deficits, environmental factors including crowded housing conditions, and/or attitude of care staff, may be associated with the emergence of BPSD.[6]

However, previous studies on the BPSD have yielded inconsistent findings. Moreover, most studies have been conducted in Western countries where no comprehensive study with a large patient sample size has been carried out.

In this study, the factors influencing BPSD in AD patients were examined using data from the Clinical Research of Dementia of South Korea (CREDOS) study.

METHODS

1. Subjects and Study Design

The CREDOS study, a prospective, cohort study, was conducted at 56 hospitals in Korea from November 2005 to May 2012. Details of the CREDOS data have been previously published.[7] This study used data from 1,737 patients who were diagnosed with AD based on criteria from the NINCDS-ADRDA (National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association) after excluding Lewy body dementia, Parkinson disease, Huntington disease, and mild cognitive impairment.

Patients with serious diseases (uncontrollable diabetes, serious liver failure, arrhythmia, advanced kidney disease, and malignancy), serious hearing impairment or visual disturbance, mental illness, neurological disease from penetrated basal ganglia, and missing blood tests or psychological tests were excluded. Finally, 1,128 patients were examined in this study. Each patients was matched to their caregiver to obtain information regarding cognition, activities of daily living, demographic characteristics, BPSD, and other comorbidities.

Caregivers of patients were defined as those who met the following conditions: (1) those who were a patient's relative, (2) those who had close relationships with patients and spent time with them regularly, and (3) those who consented to be interviewed.

All study procedures were approved by the Institutional Review Board at relevant clinical centers (#2005-02-008, ClinicalTrials.gov registration number: NCT01198093). Written informed consent was obtained from each participant.

2. Behavioral and Psychological Symptoms of Dementia Assessment

BPSD were examined by the patient caregivers using the Korean version of the Neuropsychiatric Inventory (K-NPI). The K-NPI measures 12 domains of behavioral and psychological symptoms, including delusion, hallucination, agitation/aggression, depression/dysphoria, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, night-time behavior, and appetite/eating changes. Caregivers were asked to describe the patient symptoms that had occurred during the previous 4 weeks. Caregivers were to describe the symptom frequency (scores of 1–4) and severity (scores of 1–3). Each item had scores ranging from 0 to 12 as calculated by multiplying frequency and severity.[8] The total score ranged from 0 to 144 after summing the scores for each item.

3. Neuropsychological Assessment

The Seoul Neuropsychological Screening Battery (SNSB) is a comprehensive neuropsychological test that evaluates five cognitive domains: attention, memory, language, visuospatial function, and frontal/executive function. The dementia version of Seoul Neuropsychological Screening Battery (SNSB-D) was modified from the original SNSB to assess dementia patients.[9] The SNSB-D consists of the following tests: attention (score of 0–17), language and related function (score of 0–27), visuospatial ability (score of 0–36), memory (score of 0–150), and frontal/executive function (score of 0–70). Higher scores indicate more preserved function in all sub-domains.

4. Clinical Assessment

The Korean version of Mini-Mental Status Examination (K-MMSE), Clinical Dementia Rating Sum of Box (CDR-SB), and Global Deterioration Scale (GDS) were administered. Depression was defined using the Geriatric Depression Scale consisting of 15 items.

The Barthel Index for Activities of Daily Living (Barthel-ADL) was used to evaluate the ability to accomplish basic ADLs. Scores for the Barthel-ADL range from 0 to 20. A higher score indicates greater independence.[10] In this study, the Seoul-Instrumental Activities of Daily

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Living (S-IADL) was also used to evaluate instrumental ADLs.[11] The S-IADL was developed to evaluate patient social and instrumental ADLs. All items were measured based on a four-point scale ranging from 0 to 3, with scores ranging from 0 to 24. A lower score indicates a better ability to perform social and instrumental ADLs.

A medical history of hypertension, heart disease, diabetes, gastrointestinal disease, brain surgery, anemia, arthritis, epilepsy, neuropsychiatric disease, and carbon monoxide poisoning by doctor's diagnosis, and a family history of stroke and dementia were obtained. All participants underwent brain magnetic resonance imaging and routine laboratory tests including complete blood count, blood chemistry profiles, vitamin B12 and folate levels, syphilis serology, thyroid function, and lipid level. They were also assessed for the following variables: phone (user, non-user), smoking (current, former, and non-smoker), previous alcohol use (a lot, a little, or non-drinking), current alcohol drinking (drinker, non-drinker), occupation, education, and driving. Age, caregiver sex, and presence or absence of a caregiver in the home were assessed.

5. Statistical Analyses

To evaluate the association between the K-NPI and each variable evaluated at AD diagnosis, Spearman's rank correlation analysis was used for continuous variables. The Wilcoxon signed rank-sum test for two or fewer categorical variables or the Kruskal-Willis rank test for three or more categorical variables were used. Correlations with factors influencing the K-NPI were analyzed using median regression analysis. Two-tailed tests were conducted with statistical significance set at P<0.05. STATA SE ver. 10.0 (Stata Corp., College Station, TX, USA) was used for all statistical analyses.

RESULTS

Table 1 presents the general patient characteristics. The mean patient age was 72.9 years. Males accounted for 37.8% of the patients. Patients who participated in this study had 8 years of education on average. Drinkers accounted for 21.3%, ex-smokers 20.7%, current smokers 9.1%, drivers 10.7%, and mobile phone users 58.1% of all patients. The average caregiver age was 53.3 years with 35.8% males.

Table 2 presents the correlations between the clinical or demographic characteristics and the K-NPI score. When examining the correlations between demographic and health-related behavior and the K-NPI score, patients who did not use a mobile phone, who did not have a job at the time of the survey, and who had experienced drinking heavily in the past achieved higher K-NPI scores. The association between years of education and the K-NPI score was marginally significant.

The ADL and K-MMSE scores exhibited significant negative correlations with the K-NPI. The S-IADL, CDR-SB, and GDS scores were significantly positively correlated with the K-NPI score. There was a negative correlation between the SNSB-D and K-NPI scores, with lower SNSB-D scores correlated with higher K-NPI scores.

Table 1. Clinical and demographic characteristics of the subjects (N=1,128)

Characteristic	Value
Demographic characteristics	
Age (y)	73.0±8.0
Sex (male)	37.8
Education (y)	8.2±5.1
Drinking	21.3
Ex-smoker	20.7
Current smoker	9.1
Driving	10.7
Phone	58.1
Caregiver sex (male)	35.8
Caregiver age (y)	53.3±14.7
Clinical characteristics	
Activities of daily living (total score=20)	19.3±2.0
Seoul-Instrumental Activities of Daily Living (total score=24)	16.3±9.4
Korean version of the Neuropsychiatric Inventory (total score=144)	12.5±15.5
Korean version of Mini-Mental Status Examination (total score=25)	20.1±4.4
Clinical Dementia Rating Sum of Box (total score=18)	4.8±2.6
Global Deterioration Scale (total score=7)	4.1±0.8
Diabetes mellitus	19.41
Hypertension	45.7
Heart disease	12.4

Values are presented as mean±standard deviation or %.

An abnormal level of free T4, anemia, gastrointestinal disease, and family history of stroke were correlated with the K-NPI scores. In addition, female and younger caregivers were associated with higher K-NPI scores.

Table 3 presents the results of a multivariate analysis after adjusting for age, education years, phone use, previous heavy drinking, and having an occupation in the past. The ADL score (P<0.001), K-MMSE score (P=0.003), and caregiver age (P=0.005) were negatively associated with the K-NPI. For the SNSB-D items, memory (P=0.022) and frontal and executive function (P<0.001) exhibited significant negative correlations. The significant negative associations between the K-NPI score and the SNSB-D items of attention, language, and visuospatial function were attenuated after adjusting for confounding factors. The S-IADL (P<0.001), CDR-SB (P<0.001), and GDS (P<0.001) scores exhibited positive associations with the K-NPI score.

An abnormal free T4 level (P<0.001), the presence of anemia (P<0.001), and a family history of stroke (P=0.001), and the presence of a female caregiver (P=0.004) also had significant correlations with the K-NPI score.

DISCUSSION

In this study, we comprehensively evaluated the correlation between the BPSD and demographic characteristics, health-related behavior, neuropsychological tests, blood tests, and caregiver characteristics of AD patients.

These results confirmed that BPSD in AD patients were related to

Table 2. Correlations among the clinical and demographic characteristics of patients and the scores on the Korean version of the Neuropsychiatric Inventory

Variable	Statistics	P-value
Demographics and health-related behavior		
Age (y)*	0.019	0.517
Sex (male/female)†	-0.041	0.967
Education (y)*	-0.057	0.057
Phone (use/not use)†	2.999	0.003
Previous heavy drinking†	1.977	0.048
Current alcohol drinking (drinker/non-drinker)†	-1.100	0.271
Smoking history (current smoker/ex-smoker/non-smoker)‡	2.343	0.310
Occupation_p (with/without)†	0.136	0.892
Occupation_c (with/without)†	4.132	<0.001
Clinical assessment		
Activities of daily living*	-0.257	<0.001
Seoul-Instrumental Activities of Daily Living*	0.401	<0.001
Korean version of Mini-Mental Status Examination*	-0.134	<0.001
Clinical Dementia Rating Sum of Box*	0.377	<0.001
Global Deterioration Scale*	0.296	<0.001
Neuropsychological test (Seoul Neuropsychological Screening Battery-dementia score)		
Attention*	-0.091	0.002
Language*	-0.087	0.004
Visuospatial*	-0.068	0.022
Memory*	-0.112	<0.001
Frontal and executive*	-0.154	<0.001
Known medical history (with/without)		
Diabetes mellitus†	-0.166	0.868
Hypertension†	-0.684	0.494
Heart disease†	-1.377	0.169
Head trauma†	0.173	0.863
Carbon monoxide poisoning†	-1.280	0.201
Brain surgery†	-0.354	0.724
Abnormal free thyroxine†	-2.284	0.022
Abnormal thyroid stimulating hormone†	-0.205	0.838
Anemia†	-5.502	<0.001
Arthritis†	-1.762	0.078
Epilepsy†	-1.315	0.188
Gastrointestinal disease†	-2.978	0.003
Dyslipidemia†	-1.122	0.262
Alcoholics†	-0.971	0.332
Depression†	-1.136	0.256
Previous neuropsychiatric history†	-0.621	0.534
Stroke family history (with/without)†	-3.414	<0.001
Dementia family history (with/without)†	-0.143	0.886
Caregiver		
Age (y)*	-0.099	<0.001
Sex (male/female)†	3.489	<0.001
Living (with/without)†	-0.669	0.504

Occupation_p: patient who had an occupation in the past, Occupation_c: patient who has an occupation currently.
*Continuous variables (Spearman's rank correlation coefficient, rho). †Two or fewer categorical variables (Wilcoxon signed rank-sum, Z). ‡Three or more categorical variables (Kruskal-Willis rank test, X_3^2).

various factors including patient factors and caregiver factors. In particular, patient dependency and AD severity had strong associations with BPSD. In addition, the presence of anemia; an abnormal free T4 level; a family history of stroke; and the presence of young, female caregivers were correlated with BPSD.

In previous studies measuring dementia severity using the MMSE score, a low MMSE score was correlated with the BPSD in AD patients.[12-14] Similarly, our study revealed that dementia severity exhibited significant correlations with the BPSD, although the mean MMSE score in our study was higher than that in previous studies (mean MMSE score: 20.09 in our study versus 17.8[12] versus 16.9[13] versus 13.4[14]). Overall, the severity of dementia may be correlated with the emergence of BPSD.

Among the cognitive sub-domains, memory impairment was significantly correlated with the K-NPI score. There may be several reasons for the association of memory impairment and BPSD in AD patients. First, memory function has been demonstrated to be related to the anterior cingulate.[15] The anterior cingulate may be involved in the presentation of some BPSD.[16] Our results suggested that memory was correlated with the BPSD. However, there are few studies on the correlation between the SNSB-D score and the BPSD. Therefore, it is necessary to conduct further studies.

Second, the association between psychosis and impaired cognition including performance memory,[17] semantic memory,[18] executive function,[18] short-term and delayed memory, executive functions, and information processing speed[19] can be explained by genes that impact the frontal cognitive system, including catechol-O-methyltransferase,[20] frontal brain pathology, and/or frontal metabolic deficiencies, which can be confirmed with functional imaging studies.[21]

A study investigating correlations between the Cumulative Illness Rating Scale and the NPI in dementia patients revealed that several NPI items had significant associations with medical illnesses including genitourinary and respiratory diseases.[22] Cerebrovascular diseases had significant associations with psychosis of AD, particularly delusion.[23] In our study, patients with anemia and abnormal free T4 levels obtained higher NPI scores. However, high blood pressure, which has been demonstrated to be a risk factor for cerebrovascular disease, was not significantly correlated with the K-NPI score, whereas family history of stroke was significantly correlated with the K-NPI score. Thus, further research is needed to examine these findings.

The association between thyroid function and AD has been inconsistent. Stern et al.[24] reported that thyroid stimulating hormone (TSH) and free T4 levels were not significantly associated with the BPSD in AD patients. However, a higher free T4 level was associated with atrophy of the hippocampus and amygdala on magnetic resonance imaging[25] or with greater numbers of neocortical neuritic plaques and neurofibrillary tangles.[26] Therefore, the free T4 level, rather than the TSH level, may be associated with BPSD.

A cohort study reported that a higher or lower hemoglobin level was related to AD and earlier decline in AD-related cognitive function.[27] However, few studies have investigated the correlations between anemia and the BPSD.

A recent study reported that diabetes was associated with progression from mild cognitive impairment to AD[28] and another study reported that diabetes was related to a decline in AD patient cognitive

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Table 3. Median regression analysis for the factors associated with Korean version of the Neuropsychiatric Inventory

Variable	Coefficient	Standard error	t-value	95% confidence interval	P-value
Clinical assessment					
Activities of daily living	-2.542	0.149	-17.06	-2.834 to -2.249	<0.001
Seoul-Instrumental Activities of Daily Living	0.490	0.028	17.55	0.435 to 0.545	<0.001
Korean version of Mini-Mental Status Examination	-0.294	0.098	-3.00	-0.486 to -0.102	0.003
Clinical Dementia Rating Sum of Box	1.841	0.151	12.22	1.546 to 2.137	<0.001
Global Deterioration Scale	3.596	0.502	7.17	2.612 to 4.580	<0.001
Neuropsychological test (Seoul Neuropsychological Screening Battery-dementia score)					
Attention	-0.378	0. 195	-1.94	-0.759 to 0.004	0.053
Language	-0.069	0.099	-0.69	-0.264 to 0.127	0.490
Visuospatial	-0.038	0.046	-0.81	-0.129 to 0.054	0.418
Memory	-0.064	0.028	-2.29	-0.119 to -0.009	0.022
Frontal and executive	-0.162	0.035	-4.58	-0.231 to -0.092	<0.001
Known medical history					
Abnormal free T4	17.207	3.819	4.51	9.714 to 24.700	<0.001
Anemia	4.304	0.924	4.66	2.491 to 6.118	<0.001
Gastrointestinal disease	2.75	1.492	1.84	-0.178 to 5.678	0.066
Stroke family history	2.9	0.902	3.22	1.130 to 4.670	0.001
Caregiver					
Age (y)	-0.082	0.029	-2.81	-0.140 to -0.025	0.005
Sex (male/female)	-2.522	0.864	-2.92	-4.217 to -0.827	0.004

function.[29] In this study, diabetes was not significantly correlated with AD behavioral and psychological symptoms. We suggest that this was because the enrolled diabetes patients may have been well-controlled, or their diabetes history was obtained from a self-administered questionnaire, not from fasting glucose or hemoglobin A1C measurements. Thus, it is necessary to carry out further research on the relationships between diabetes and the BPSD.

The patient-caregiver relationship can have an effect on BPSD in AD patients.[30] Although we did not assess the patient-caregiver emotional relationship and communication, we found that the young caregivers were associated with higher K-NPI scores. This may be attributed to differences in the quality of care provided by caregivers due to experience, emotional relationships, or familiarity.

Additionally, in our study, caregiver age, sex, and family history of stroke were associated with the BPSD. These are meaningful as risk factors and these findings warrant further research in the future.

Our study has several strengths. First, we confirmed our hypothesis with a large national sample from 56 hospitals in Korea. There have been several studies on the factors influencing BPSD, but the results were inconsistent. However, those studies enrolled small populations. Second, a wide range of variables that were related to AD development or deterioration were evaluated according to patient and caregiver factors including demographics, health-related behavior, and clinical and neuropsychological tests. Our findings that more severe AD, lower frontal lobe function, anemia, and thyroid dysfunction were related to BPSD severity had been demonstrated in other studies; hence, we confirmed those results in data for large population.

The study also had some limitations. First, the findings cannot be generalized to other types of dementia patients, because this study was confined to AD patients. Indeed, the medications for AD and their effect, patient's mood, sleep, general nutritional status, care environment and quality, and communication between patients and caregivers may be more important risk factors for the BPSD. However, this study did not cover all possible risk factors such as medication history, including the use of cholinesterase inhibitors, or physical activity level, which were not surveyed in the CREDOS study. Additionally, blood test results were merely classified into normal or abnormal.

In conclusion, AD patients exhibited various risk factors for BPSD, including the inability to live an independent life and AD severity. We comprehensively examined many factors that were predicted to be associated with the BPSD. These findings suggest that a comprehensive strategy for the prevention and treatment of BPSD is important for AD patients.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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