

Hypertension and Neuropsychiatric Symptoms in Patients with Drug-Naïve Alzheimer's Disease

Inha Hwang,^{1*} Kyoung-Hwa Baek,^{2*} Jeong Ho Han,¹ Sang-Won Ha,¹ YoungSoon Yang¹

¹Department of Neurology, Veterans Health Service Medical Center, Seoul, Korea

²Department of Nursing, Gyeongbuk College of Health, Gimcheon, Korea

Background and Purpose Neuropsychiatric symptoms (NPS) such as anxiety, depression, and delusions affect up to 90% of all patients with Alzheimer's disease (AD). NPS is associated with significant caregiver burden and patient distress. Given the severe burden of NPS in AD, it is critical to know potential modifiable risk factors of NPS in AD. This study explores the association between hypertension and NPS in patients with drug-naïve AD.

Methods We reviewed medical records of 149 patients with AD with ($n=80$) and without ($n=69$) hypertension. NPS were assessed using the Korean version of Neuropsychiatric Inventory (K-NPI). Affective, psychotic, and behavior symptom clusters were assessed separately.

Results The total score of K-NPI was not significantly different between patients with AD with and without hypertension. Among K-NPI domains, scores of depression/dysphoria ($p=0.045$), anxiety ($p=0.022$), and apathy/indifference ($p=0.037$) were significantly higher in patients with AD with hypertension. Systolic blood pressure (BP) was associated with higher total K-NPI and affective symptom cluster scores. Diastolic BP was associated with affective symptom cluster scores.

Conclusions Results suggest that hypertension increases risk of specific NPS in patients with AD. Among NPS, hypertension was associated with affective symptom cluster.

Key Words hypertension, Alzheimer's disease, neuropsychiatric symptoms.

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Correspondence: YoungSoon Yang, MD, Department of Neurology, Veterans Health Service Medical Center, 53 Jinhwangdo-ro 61-gil, Gangdong-gu, Seoul 05368, Korea

Tel: +82-2-2225-4106, **Fax:** +82-2-2225-4105, **E-mail:** astro76@naver.com

*These authors contributed equally to this work.

INTRODUCTION

Hypertension and dementia are common diseases in the elderly population. Approximately 8–10% of people age 65 or older suffer from dementia and 65% suffer from hypertension.^{1,2} In recent epidemiological studies, vascular risk factors have been associated with Alzheimer's disease (AD) as well as vascular dementia. In particular, hypertension is a major vascular risk factor, and studies on the relationship between hypertension, cognitive dysfunction, and onset of dementia are

actively underway. Some cross-sectional observational studies have reported cognitive decline occurs frequently when blood pressure (BP) is high, especially when uncontrolled.³ Other studies have reported hypertension and cognitive function are correlated as U-curves, and that both very high and very low BP increase cardiovascular disease and consequently cognitive decline.^{4,5} In most follow-up studies, middle-aged hypertension was an independent risk factor for senile cognitive impairment and dementia.^{6–9}

However, little is known about the relationship between modifiable risk factors and neuropsychiatric symptoms (NPS) in AD. Vascular risk factors, such as hypertension, hyperlipidemia, and stroke, are of interest because they are risk factors for NPS among individuals without AD.¹⁰ We investigated prevalence of NPS and the degree of Korean version of Neu-

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ropsychiatric Inventory (K-NPI) domain according to presence or absence of hypertension in patients with AD.

METHODS

Participant screening

This study was designed to retrospectively review medical records to evaluate prevalence of dementia at the Veterans Health Service Medical Center in Korea August 2011–August 2014, for a maximum of 3 years. Data were reviewed from the time of the first diagnosis of dementia. Patients with AD were selected according to criteria for ‘probable AD’ of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association.¹¹ Patients with a history of head injury, mental illness, alcoholism, substance abuse, or other neurological or medical disorders that may impair cognitive function were excluded from the study. Patients were divided into two groups according to presence or absence of hypertension, and sociodemographic differences between patients and caregivers, memory, depression, and behavioral psychological symptoms were compared in each group. Presence of hypertension was documented by medical history. Participants with systolic BP more than 140 mm Hg and/or a diastolic BP more than 90 mm Hg were classified as hypertensive. A total of 149 subjects were enrolled in this study, 80 patients with AD with hypertension and 69 patients with AD without hypertension.

Clinical assessments

Patients were assessed by the Korean version of the Mini Mental State Examination (K-MMSE) to determine overall cognitive function.^{12,13} Overall disease progression was assessed using the Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) score.¹⁴ For evaluation of NPS, 12 domains were analyzed using the K-NPI.¹⁵ The 12 domains were delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, night-time behavior disturbances, and appetite/eating abnormalities. We examined the total score of K-NPI, the score of each domain of K-NPI, and prevalence. For primary endpoints, we assessed prevalence of NPS in patients with AD with or without hypertension. For secondary endpoints, we examined the extent to which domains of K-NPI correlated with hypertension in patients with AD. This study was approved by the Institutional Review Board of Veteran Health Service Medical Center and met standards established by the Declaration of Helsinki (IRB No. 2015-04-001).

Data analysis

Collected data were analyzed using Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM Corp., Armonk, NY, USA). Two-group homogeneity tests were analyzed by χ^2 -test, Fisher’s exact test, and Paired *t*-test, and differences in NPS between the two groups were analyzed by Paired *t*-test. Principal component factor analysis was used to test validity of K-NPI. The relationship between NPS, domains of K-NPI, and hypertension was analyzed by Pearson’s correlation. The *p* values of less than 0.05 were considered to indicate statistically significant differences.

RESULTS

Homogeneity test of general characteristics and dependent variables between two groups

A total of 149 subjects were enrolled in this study, 80 of whom were patients with AD with hypertension and 69 patients with AD without hypertension. Table 1 compares clinical characteristics of patients with AD with and without hypertension. There was no statistically significant difference in sex ratio, duration of education, progression of dementia, cognitive function test between two groups. Both groups revealed homogeneity in general characteristics except for age.

Prevalence of domain scores of K-NPI in patients within two groups

Mean total score of K-NPI was higher in patients with AD with hypertension than without hypertension, but was statistically insignificant. In all domains except of night-time behavior disturbances, mean score was higher in patients with

Table 1. Homogeneity test of general characteristics and dependent variables between two groups (*n*=149)

Characteristics	AD+HTN (n=80)	AD (n=69)	<i>p</i>
	Mean±SD or <i>n</i> (%)		
Age (years)	70.9±7.4	73.5±7.5	0.041
Female gender (%)	49 (61.3)	45 (65.2)	0.097
Education (years)	9.4±7.4	10.5±5.0	0.235
K-MMSE	23.3±5.3	22.6±4.7	0.202
CDR-SOB	3.0±2.8	3.5±2.8	0.226
CDR, <i>n</i>			0.596*
0.5	55 (68.7)	45 (65.2)	0.956
1	20 (25)	20 (29)	
2	5 (6.3)	4 (5.8)	

*Fisher’s exact test.

AD: Alzheimer’s disease, CDR: Clinical Dementia Rating Scale, CDR-SOB: Clinical Dementia Rating Scale Sum of Boxes, HTN: hypertension, K-MMSE: Korean version of the Mini-Mental State Examination, SD: standard deviation.

AD with hypertension than that in patients with AD without hypertension. In particular, there was a statistically significant difference in the domains of depression/dysphoria ($p=0.045$), anxiety ($p=0.022$), and apathy/indifference ($p=0.037$) (Table 2).

Exploratory factor analysis with an extraction of three factors

To verify construct validity and classify a number of variables by homogeneous factor, an exploratory factor analysis was conducted. As the goodness-of-fit of the sample (Kaiser-Meyer-Olkin, KMO) was 0.818 and Bartlett sphericity test was statistically significant, factor analysis was conducted. Active ingredient factor analysis was used, and because correlation between factors was not assumed, orthogonal rotation and Varimax method were used. Since commonness by question was not less than 0.4, no deleted question was found. As these criteria were applied, factors of which characteristic value determining number of factors not less than 1 was identified, and the final 3 factors were extracted. Factor 1 described 26.5% of distribution percentage with 5 questions, and the level of confidence was $\alpha=0.787$, named psychotic symptom cluster. Factor 2 described 19.3% of distribution percentage with 3 questions, and level of confidence was $\alpha=0.826$, named behavior symptom cluster. Factor 3 describes 18.9% of distribution percentage with 4 questions, level of confidence is $\alpha=0.739$, named affective symptom cluster. Each factor was named K-NPI factor. Total accumulated distribution percentage was 64.858 (Table 3).

Table 2. Prevalence of domain scores of K-NPI in patients with two groups ($n=149$)

Characteristics	AD+HTN (<i>n</i> =80)	AD (<i>n</i> =69)	<i>p</i>
	Comp-S mean±SD		
1. Delusion	0.60±1.985	0.30±1.019	0.246
2. Hallucination	0.40±1.420	0.17±0.085	0.212
3. Agitation/aggression	0.45±1.066	0.43±0.119	0.929
4. Depression/dysphoria	1.91±2.499	1.09±2.015	0.045
5. Anxiety	1.84±2.367	0.72±1.371	0.022
6. Euphoria/elation	0.18±0.938	0.06±0.291	0.321
7. Apathy/indifference	1.79±2.715	0.63±2.072	0.037
8. Disinhibition	0.56±1.422	0.35±0.937	0.287
9. Irritability/lability	1.26±2.509	1.10±2.001	0.669
10. Aberrant motor	0.51±1.793	0.42±1.288	0.723
11. Night-time behavior	1.25±2.588	1.43±2.709	0.671
12. Appetite/eating	1.19±2.211	1.19±2.788	0.998
Total K-NPI Scores	10.24±16.731	8.61±9.789	0.463

AD: Alzheimer's disease, Comp-S: composite score (frequency $\times$ severity), HTN: hypertension, K-NPI: Korean version of Neuropsychiatric Inventory, SD: standard deviation.

Correlation between K-NPI/K-NPI factor and variables

There was a strong correlation between K-NPI and K-NPI factors. There was correlation between K-NPI and CDR-SOB, and between K-NPI and K-MMSE. Systolic hypertension was correlated with K-NPI, and in particular, to the affective symptom cluster of the three factors. Diastolic hypertension was also correlated with the affective symptom cluster. There-

Table 3. Exploratory factor analysis with an extraction of three factors ($n=149$)

Items of K-NPI	Factor loadings		
	Factor 1	Factor 2	Factor 3
3. Agitation/aggression	0.808		
8. Disinhibition	0.793		
2. Hallucination	0.770		
1. Delusion	0.714		
9. Irritability/lability	0.654		
6. Euphoria/elation		0.802	
11. Night-time behavior		0.699	
10. Aberrant motor		0.658	
12. Appetite/eating			0.839
7. Apathy/indifference			0.711
4. Depression/dysphoria			0.658
5. Anxiety			0.638
Factor correlations			
Factor 1	1	0.491*	0.473*
Factor 2		1	0.514*
Cronbach's α	0.787	0.826	0.739
Eigen values	3.186	2.317	2.279
Variance explained (%)	26.550	19.311	18.996
Total variance explained (%)	26.550	45.892	64.858
Keiser Meyer Olkin			0.835
Bartlett's test of sphericity	$\chi^2=795.204$, df (p)=45, $p<0.001$		

* $p<0.01$. K-NPI: Korean version of Neuropsychiatric Inventory.

Table 4. Correlation between K-NPI/K-NPI factors and variables

	K-NPI	Factor 1	Factor 2	Factor 3
K-NPI				
Factor 1	0.800*			
Factor 2	0.758†	0.491†		
Factor 3	0.865†	0.473†	0.514†	
CDR-SOB	0.359†	0.254†	0.330†	0.329†
K-MMSE	-0.198*	-0.064*	-0.182*	-0.232*
Systolic BP (mm Hg)	0.216*	0.014	-0.140	0.551†
Diastolic BP (mm Hg)	-0.780	0.370	0.220	0.179*

* $p<0.05$, † $p<0.01$.

BP: blood pressure, CDR-SOB: Clinical Dementia Rating Scale Sum of Boxes, K-NPI: Korean version of Neuropsychiatric Inventory, K-MMSE: Korean version of the Mini-Mental State Examination.

fore, hypertension was related to NPS in AD patients and was associated with affective symptom cluster of the NPS (Table 4).

DISCUSSION

In this study, total score of K-NPI was not significantly different between patients with AD with and without hypertension. However, hypertension was associated with specific domains of K-NPI, depression/dysphoria ($p=0.045$), anxiety ($p=0.022$), and apathy/indifference ($p=0.037$). It was also associated with the affective symptom cluster but not with psychotic or behavior symptom clusters. A previous study in a cross-sectional sample of 254 participants with AD followed in the Cache County Study on Memory in Aging, hypertension was associated with 2–3 times increased risk for delusions, anxiety, and agitation/aggression.¹⁰ A recent study has found that hypertensive patients with AD had increased NPS burden compared with normotensive patients with AD.¹⁶ Another recent study in a large cohort of 457 patients with AD revealed a history of hypertension was associated with worse NPS as measured by the Neuropsychiatric Inventory Questionnaire at the time of AD diagnosis.¹⁷ However, in one longitudinal study in a community-based AD cohort, no clear relationship was found between individual vascular risk factor and NPS in AD, but use of antihypertensive medication more than four times per week was associated with higher total neuropsychiatric inventory and affective cluster scores in AD.¹⁸ Different results between these studies are probably due to differences in study methods, including study subjects (normotensive vs. hypertensive subjects), BP measurement (single outpatient monitoring vs. mobile BP monitoring), antihypertensive use, presence of other vascular risk factors, and differences in cognitive function and dementia selection criteria.

Pathophysiology of how hypertension relates to NPS in AD is unclear. A possible explanation for association between hypertension and NPS is that cerebral blood flow may be decreased in prefrontal and temporal cortices.¹⁹ Another study suggests that hypertension can increase risk of cerebrovascular disease, that may increase incidence of depression in dementia.²⁰ Hypertension is related to cerebrovascular disease and vascular dementia based on vascular remodeling.²¹ However, much is unknown about mechanisms of linking hypertension to AD. Although exact mechanisms are not fully understood, increasing evidence suggests vascular risk factors including hypertension may be associated with AD.^{22–24} Pathophysiological processes between hypertension and AD may involve inflammatory processes, blood-brain barrier dysfunction, and hypoperfusion.^{25–27} Evidence suggests that as a result of hypertension, chronic oligemia may downregulate synthe-

sis of proteins necessary for synaptic plasticity and memory formation, and promote neuronal tau phosphorylation, β -amyloid oligomerization, and upregulation of amyloidogenic amyloid precursor protein.^{28,29} Each of these neurophysiological changes likely contributes to development of AD.

Results of this study suggest hypertension increases risk of specific NPS in patients with incident of AD. Among NPS, hypertension was associated with affective symptom cluster. Therefore, if an affective symptom is observed in patients diagnosed with AD, it may be necessary to investigate whether the patient has vascular risk factor such as hypertension. Effective management of hypertension can potentially play a therapeutic role in mitigation of NPS in AD. Given the severe burden of NPS in AD, further study on effects of modifiable risk factors and antihypertensive medications in AD are of interest. In addition, identifying potential modifiable risk factors for AD is crucial for primary prevention and may reduce incidence of AD.

Several limitations of this study exist. First, this was a limited study using single centre dementia registry. However, composition and ratio of NPS was consistent with many other studies. Second, there was insufficient control of antihypertensive therapy and vascular comorbidities. Several patients in our sample were on antihypertensive medication that may underestimate negative impact of hypertension on NPS. Other vascular risk factors such as diabetes or obesity may independently influence AD pathology. Finally, this was a retrospective, cross-sectional, and observational study. Further longitudinal studies whether prevention of hypertension could attenuate NPS are needed.

Conflicts of Interest

The authors have no financial conflicts of interest.

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