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Frequency of depressive syndromes in elderly
individuals with no cognitive impairment, mild
cognitive impairment, and Alzheimer's disease
dementia in memory clinic setting

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Abstract

Frequency of depressive syndromes in elderly individuals with no cognitive impairment, mild cognitive impairment, and Alzheimer's disease dementia in memory clinic setting

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Introduction: The aims of this study were to investigate the frequency of various depressive syndromes in elderly individuals with no cognitive impairment (NC), mild cognitive impairment (MCI),

and Alzheimer's disease dementia (AD) in a memory clinic setting, and then to test whether severe and milder forms of depressive syndromes are differentially associated with the cognitive groups.

Methods: Two hundred and sixteen NC, 478 amnesic MCI, and 316 AD subjects were included in the study. We investigated the frequency of depressive syndromes, defined by three different categories: major depressive disorder (MaDD) and minor depressive disorder (MiDD), according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, and depression, according to the provisional diagnostic criteria for depression in Alzheimer's disease (NIMH-dAD).

Results: The overall frequency of each depressive syndrome was 5.4% for MaDD, 16.9% for MiDD, and 29.6% for NIMH-dAD. The frequencies of MaDD were 6.9% in the NC, 4.6% in the MCI, and 5.7% in the AD subgroup. Those of MiDD were 10.2% in the NC, 17.8% in the MCI, and 20.3% in the AD subgroup. The respective frequencies of NIMH-dAD were 20.4%, 29.7%, and 35.8%. While the frequency of MaDD did not show any significant difference

among cognitive subgroups, those of MiDD and NIMH–dAD, i.e., relatively milder depressive syndromes, showed significant group differences, with a gradual increase from NC to AD.

Conclusions: Our results of the differential associations of various depressive syndromes with the cognitive impairment groups suggested that milder form of depression is influenced by Alzheimer–related neurodegenerative process, while severe form of depressive syndrome is not associated with such process.

Keywords: depressive syndrome; frequency; mild cognitive impairment; Alzheimer’s disease dementia; memory clinic

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List of Abbreviations

AD: Alzheimer's disease Dementia

ADL: Activities of Daily Living

ANOVA: Analysis of Variance

BNT: Boston Naming Test

CADD: Clinical Assessment of Depression in Dementia

CDR: Clinical Dementia Rating

CERAD-K: Consortium to Establish a Registry for Alzheimer's disease

CI: Confidence Interval

CP: Constructional Praxis

CR: Constructional Recall

CSNMD: Clinically Significant Non-Major Depression

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition

FAB: Frontal Assessment Battery

GDS: Geriatric Depression Scale

HRSD: Hamilton Rating Scale for Depression

MaDD: Major Depressive Disorder

MCI: Mild Cognitive Impairment

MDE: Major Depressive Episode

MiDD: Minor Depressive Disorder

MMSE: Mini–Mental State Examination

MRI: Magnetic Resonance Imaging

NC: No Cognitive Impairment

NIMH: National Institute of Mental Health

NIMH–dAD: National Institute of Mental Health provisional criteria for depression in AD

NINCDS–ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association

OR: Odds Ratio

SCID: Structured Clinical Interview for DSM

SF: Semantic Fluency

SCWT: Stroop Color Word Test

VRS: Vascular Risk Score

WLM: Word List Memory

WLR: Word List Recall

WLRc: Word List Recognition

I. Introduction

Depression is a very common neuropsychiatric manifestation in patients with Alzheimer's disease dementia (AD) (1, 2). While other neuropsychiatric problems, such as delusions, hallucinations, agitation, and apathy, occur mainly in the later stages of AD, depression is frequent even in the very early stage of the disease (3). Individuals with mild cognitive impairment (MCI), known as the prodromal or high-risk stage of AD, also frequently experience depression. Depression in AD is associated with several adverse consequences, including negative influences on the patients' quality of life and activities of daily living (ADL), early requirements for hospitalization, and increased caregiver burden (4, 5). In MCI patients, depression is associated not only with negative clinical impacts but also with an increased risk for conversion to AD (6).

Although many studies have reported the frequency of depressive symptoms in AD and MCI, relatively few have

investigated the prevalence of depressive syndromes defined according to formal diagnostic criteria in AD (2, 4, 7–11) and MCI (12, 13). Moreover, no previous study has compared the frequency of depressive syndrome across the spectrum of the cognitive continuum, including normal aging, MCI, and AD. Clinically meaningful depressive phenomena are more likely to manifest as a syndrome rather than individual elementary symptoms. The report from the European Alzheimer’s Disease Consortium suggested that a syndromal approach to neuropsychiatric manifestations of dementia can provide more insight into the association between clinical phenomena and their underlying biological mechanisms (14), and a series of studies on the biological correlates of the neuropsychiatric manifestations of dementia support this (15).

Depression in AD has several distinct clinical characteristics compared with primary depression, which is typically defined as major depressive disorder (MaDD) of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM–IV) (16). With depression in AD, the severity of symptoms and signs is milder, and irritability and social isolation are observed more frequently,

compared with primary depression. Additionally, a waxing and waning pattern is more common. A group convened by the National Institutes of Mental Health (NIMH) proposed diagnostic criteria for depression in AD (NIMH-dAD) which reflected the mild and fluctuating characteristics and common symptoms of depression in AD (1). They proposed the criteria in order to lead researchers to a better understanding of depression in AD. A couple of studies reported the frequency of NIMH-dAD (30–45%) in AD (8, 9), while there has been no reported investigation on the frequency of the same syndrome in MCI or normal aging populations. Minor depressive disorder (MiDD) is another milder form of depressive syndrome, which does not meet the full criteria for MaDD (16). To make the diagnosis of MiDD, only two to four depressive symptoms need to be present for 2 weeks, while the criteria for MaDD require at least five depressive symptoms (16).

Information on the association between the frequency of depressive syndromes and stage of cognitive decline related to Alzheimer's disease could provide insight into the underlying

biological mechanisms of the depressive syndromes. A couple of previous studies suggested that while severe form of depressive syndrome, such as MaDD, is more often a chronic mood problem which stems from vulnerability factors to mood dysregulation, milder syndromes are more influenced by physical conditions, neurodegenerative changes, and psychosocial factors frequently experienced in later life (17, 18).

In this study, we first aimed to investigate the frequencies of various depressive syndromes cross-sectionally, defined separately according to the DSM-IV MaDD and MiDD and NIMH-dAD criteria, in elderly individuals with no cognitive impairment (NC), MCI, and AD in a memory clinic setting, and then to test whether severe and milder form of depressive syndromes are differentially associated with the cognitive groups. Based on the suggestions of literature and our own clinical observations, we hypothesized that the frequency of milder form of depressive syndromes, such as MiDD or NIMH-dAD, increase from NC to AD group, and that the frequency of MaDD is constant without significant difference among cognitive groups.

II. Materials and Methods

1. Subjects

Study subjects were recruited among the individuals who visited the Dementia and Age-Associated Cognitive Decline Clinic of the Seoul National University Hospital to get clinical services or voluntarily participate in a program for early detection and management of dementia. In this study, 216 NC, 478 MCI, and 316 AD subjects were included. The AD patients met the criteria of probable AD of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) and the criteria for dementia of DSM-IV. All individuals with MCI met the current consensus criteria for amnesic MCI: 1) memory complaint confirmed by an informant, 2) objective memory impairment, 3) preserved global cognitive function, 4) independence in functional activities, and 5) not demented (19). All MCI individuals had an

overall clinical dementia rating (CDR) (20) of 0.5. In terms of criterion 2, the age-, education-, and gender-adjusted z score for at least one of the four episodic memory tests was below -1.5 . These memory tests were the Word List Memory (WLM), Word List Recall (WLR), Word List Recognition (WLRc), and Constructional Recall (CR) tests included in the Korean version of the Consortium to Establish a Registry for Alzheimer's disease (CERAD-K) neuropsychological battery (21, 22). The NC group consisted of subjects whose age-, education-, and gender-adjusted z score for all eight cognitive tests in the CERAD-K neuropsychological battery was above -1.5 .

Exclusion criteria for all subjects were any serious medical or neurological diseases present that could affect mental function, evidence of focal brain lesions on magnetic resonance imaging (MRI), the presence of severe behavioral or communication problems that would make a clinical examination difficult, and the absence of a reliable informant. Individuals with minor physical abnormalities (e.g., diabetes with no serious complications, essential hypertension, and mild hearing loss) were included. The

Institutional Review Board of the Seoul National University Hospital, Korea, approved the study, and subjects or their legal representatives gave written consent.

2. Cognitive assessments

All patients were examined by psychiatrists who had advanced training in dementia research according to the protocol of the CERAD–K clinical assessment packet. Psychiatric, general physical and neurological examinations were performed along with routine laboratory tests and MRI of the brain. Reliable informants were interviewed to acquire accurate information regarding the cognitive, emotional, and functional changes as well as the medical history of the patients. A panel consisting of four psychiatrists with expertise in dementia and depression research made clinical decisions after reviewing all available data.

Subjects also received a comprehensive neuropsychological assessment battery, which included the eight tests in the CERAD–K neuropsychological battery: Semantic Fluency (SF), ‘animal

category', the 15-item Boston Naming Test (BNT), Mini-Mental State Examination (MMSE), WLM, WLR, WLRc, Constructional Praxis (CP), and CR. The Stroop Color Word Test (SCWT) and Frontal Assessment Battery (FAB) (23) were also used to assess executive function.

3. Depression assessment

Depression was assessed using the clinical assessment of depression in dementia (CADD), a structured diagnostic interview that was designed to diagnose and characterize the number, onset, and course of major depressive episodes in AD populations (2). The CADD incorporates a structured, anchored version of the 17-item Hamilton Rating Scale for depression (HRSD) that has been validated for use in this population (24), the subsection of the Neuropsychiatric Inventory that assesses the presence/absence, frequency, and severity of a list of hallucinations and delusions that are commonly experienced by patients with dementia (25), and the portion of the Structured Clinical Interview for DSM-III-R (SCID)

that scores signs and symptoms required for the diagnosis of MaDD into a single coherent clinical interview (26). We made some modifications to the SCID portion to diagnose depressive syndromes, including MaDD, MiDD, and NIMH-dAD. MaDD was finally diagnosed according to the DSM-IV criteria, and MiDD was diagnosed according to the DSM-IV research criteria. NIMH-dAD (1) was diagnosed by the provisional diagnostic criteria for depression in Alzheimer's disease proposed by the NIMH. The criteria reflected the mild and fluctuating course of the depression in AD and included additional depressive symptoms that are common in AD patients: irritability and social isolation. The number of past major depressive episode (MDE) was also assessed during the interview, and used in the analyses as a categorical variable with categories '0' , '1' , and '2 or more' . In addition to CADD, the 30-item Korean version of the geriatric depression scale (GDS) (27, 28) was applied to all subjects.

4. Vascular risk assessment

The presence or absence of six cerebrovascular risk factors, including stroke, diabetes, dyslipidemia, transient ischemic attack, hypertension, and coronary artery disease, was assessed systematically from subjects and subjects' histories provided by the informant as well as a review of pertinent medical records. To calculate an overall measure of cerebrovascular burden, we created a composite score, i.e., the vascular risk score (VRS), which was the sum of the factors present, ranging from 0 to 6 and reported as a percentage (29).

5. Statistical analysis

The demographic, clinical, and neuropsychological characteristics of the NC, MCI, and AD groups were compared using a linear by linear association method for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. For *post hoc* analyses with one-way ANOVA, we used Tukey's method for multiple comparison corrections.

To test whether severe and milder forms of depressive syndromes are differentially associated with the cognitive groups, we tested multiple logistic regression models including each depressive syndrome as a dependent variable and cognitive group as an independent variable. Three models were tested for each depressive syndrome: model 1 included age, gender, and years of education as covariates; model 2 included VRS as a covariate as well as age, education, and gender; model 3 included the number of past MDE as a covariate in addition to the covariates of model 2. Odds ratio (OR) for the independent variable was calculated, assuming NC group as a reference group. Values with $p < 0.05$ were regarded as significant.

Psychotropic medications could affect the current state of depression. Therefore, in order to verify the validity of the results, sensitivity analysis was performed for the subgroup of participants who did not use any psychotropic medication. All analyses were performed using the SPSS software (ver. 19; SPSS, Inc.).

III. RESULTS

1. Demographic, vascular, and cognitive characteristics

Demographic, vascular, and cognitive characteristics of subjects are summarized in Table 1. The proportion of women was 69.2% and the mean age was 73 years for all subjects. There was no significant difference in the gender ratio among the NC, MCI, and AD subgroups, but age and years of education showed differences among groups. NC subjects were significantly younger and more educated compared with the other groups. VRS was higher in the MCI than AD subgroup, while there was no significant VRS difference between NC and MCI or between NC and AD. Neuropsychological test scores showed significant group differences, with a gradual decrease from NC to AD, as expected.

Table 1. Demographic, vascular, and cognitive characteristics of the subjects

Groups	NC(<i>n</i> =216)	MCI(<i>n</i> =478)	AD(<i>n</i> =316)	F or χ^2	<i>p</i>
Gender: Female, N (%)	144 (66.7)	335 (70.1)	220 (69.6)	0.414	0.520
Age, year	69.9 (5.9)	72.9 (6.4)	74.0 (7.0)	26.53	<0.001*,†
Education, years	9.7 (5.3)	8.5 (5.2)	8.5 (5.4)	4.71	0.009*,†
CDR					
0	95 (44.0)	0 (0)	0 (0)		
0.5	121 (56.0)	478 (100)	146 (46.2)		
1	0 (0)	0 (0)	133 (42.1)		
≥ 2	0 (0)	0 (0)	37 (11.7)		
VRS, %	14.4 (13.3)	16.7 (15.9)	11.8 (13.1)	10.84	<0.001‡
NP test					
SF	15.0 (4.3)	11.0 (3.7)	7.7 (3.9)	228.21	<0.001*,†,‡
BNT [0-15]	11.8 (2.5)	9.6 (2.9)	7.2 (3.4)	153.48	<0.001*,†,‡
MMSE [0-30]	26.6 (3.1)	22.4 (4.1)	16.2 (5.7)	367.45	<0.001*,†,‡
WLM [0-30]	17.9 (3.9)	12.3 (3.9)	8.4 (4.5)	340.59	<0.001*,†,‡
CP [0-11]	10.1 (1.5)	9.1 (1.9)	8.0 (2.7)	61.68	<0.001*,†,‡
WLR [0-10]	6.2 (1.9)	2.9 (1.9)	1.0 (1.4)	545.29	<0.001*,†,‡
WLRc [0-10]	9.2 (1.3)	6.7 (2.5)	3.9 (2.9)	314.53	<0.001*,†,‡
CR [0-11]	6.9 (3.0)	3.0 (2.7)	1.2 (1.8)	328.37	<0.001*,†,‡
Stroop C	54.0 (20.1)	45.9 (16.7)	34.7 (20.4)	72.56	<0.001*,†,‡
Stroop W	64.0 (24.5)	55.0 (21.5)	42.8 (24.6)	56.83	<0.001*,†,‡
Stroop CW	34.8 (15.1)	25.2 (12.3)	16.7 (13.4)	120.50	<0.001*,†,‡
FAB [0-18]	14.3 (4.5)	12.1 (3.5)	9.5 (7.3)	57.68	<0.001*,†,‡

Note: Data for continuous variables are presented as means (standard deviation) and analyzed through one-way ANOVA with F values presented in the table. Categorical variables are presented as N (%) and analyzed through χ^2 test with the χ^2 values presented in the table. Pairs with significant group differences according to *post hoc* analysis using Tukey's method: * NC vs MCI, †NC vs AD, ‡MCI vs AD.

Abbreviations: NC, no cognitive impairment, MCI, mild cognitive impairment; AD, Alzheimer's disease dementia; CDR, clinical dementia rating; VRS, vascular risk score; NP, neuropsychological; SF, semantic fluency; BNT, Boston naming test; MMSE, mini-mental state examination; WLM, word list memory; CP, constructional praxis; WLR, word list recall; WLRc, word list recognition; CR, constructional recall; Stroop C, Stroop color; Stroop W, Stroop word; Stroop CW, Stroop color word; FAB, frontal assessment battery

2. Frequency of depressive syndromes and severity of depression

Table 2 shows the frequency of depressive syndromes and the severity of depression in the whole study population and each cognitive group. In the subjects overall, the frequencies of MaDD, MiDD, and NIMH-dAD were 5.4%, 16.9%, and 28.4%, respectively. The frequencies of MaDD were 6.9% in the NC, 4.6% in the MCI, and 5.7% in the AD subgroups. Those of MiDD were 10.2%, 17.8%, and 20.3% in the NC, MCI, and AD subgroups, respectively. The respective frequencies of NIMH-dAD were 20.4%, 29.7%, and 35.8%. While the frequency of MaDD did not show any significant difference among cognitive groups ($\chi^2 = 0.22$, $p = 0.637$), those of MiDD and NIMH-dAD, i.e., the relatively milder depressive syndromes, showed significant group differences, with a gradual increase from NC to AD ($\chi^2 = 8.55$, $p = 0.003$ for MiDD; $\chi^2 = 14.25$, $p < 0.001$ for NIMH-dAD). The frequency of past MDE decreased gradually from NC to AD. Overall, the severity of depression, as shown by the mean scores of GDS, also showed a gradual increase from NC to AD ($F = 3.56$, $p = 0.029$). The mean score of HRSD, however, did not show any difference among groups.

Table 2. Frequency of depressive syndromes and severity of depression

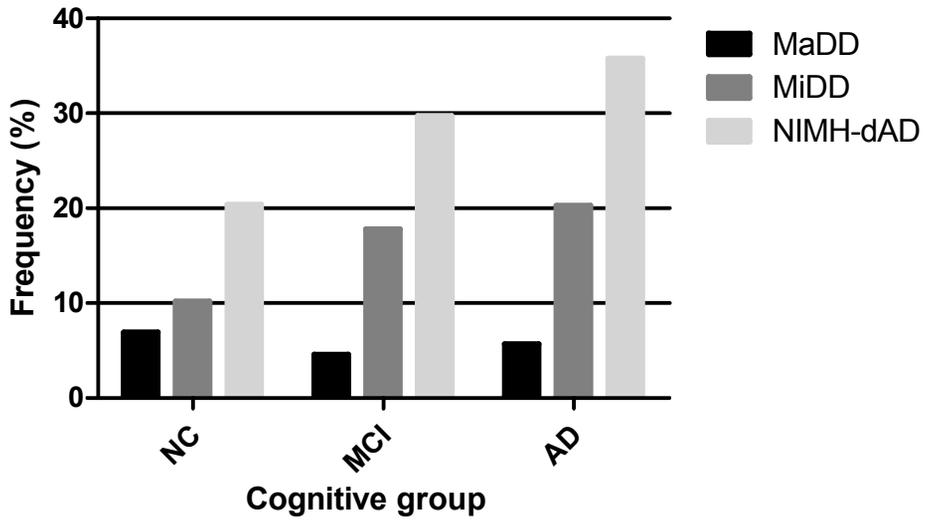
Groups	NC (n = 216)	MCI (n = 478)	AD (n = 316)	F or χ^2	P
Frequency, N (%)					
MaDD	15 (6.9)	22 (4.6)	18 (5.7)	0.22	0.637
MiDD	22 (10.2)	85 (17.8)	64 (20.3)	8.55	0.003
NIMH-dAD	44 (20.4)	142 (29.7)	113 (35.8)	14.25	<0.001
Number of past MDE, N (%)					
0	170 (78.7)	424 (88.7)	297 (94.0)		
1	39 (18.1)	46 (9.6)	16 (5.1)		
≥2	7 (3.2)	8 (1.7)	3 (0.9)		
Depression Scale					
HRSD [0-68]	4.2 (5.4)	4.4 (4.8)	5.0 (4.5)	1.68	0.290
GDS [0-30]	11.1 (7.3)	12.2 (7.1)	12.7 (6.9)	3.56	0.029†

Note: Data for continuous variables are presented as means (standard deviation) and analyzed through one-way ANOVA with F values presented in the table. Categorical variables are presented as N (%) and analyzed through linear by linear association with the χ^2 values presented in the table.

Pairs with significant group differences according to *post hoc* analysis using Tukey's method: †NC vs AD.

Abbreviations: NC, no cognitive impairment; MCI, mild cognitive impairment; AD, Alzheimer's disease dementia; NIMH-dAD, National Institute of Mental Health provisional criteria for depression in AD; MaDD, major depressive disorder; MiDD, minor depressive disorder; MDE, major depressive episode; HRSD, Hamilton Rating Scale for depression; GDS, Geriatric Depression Scale

Figure. Frequency of depressive syndromes according to cognitive groups



Abbreviations: NC, no cognitive impairment; MCI, mild cognitive disorder; AD, Alzheimer's disease dementia; NIMH-dAD, National Institute of Mental Health provisional criteria for depression in AD; MaDD, major depressive disorder; MiDD, minor depressive disorder

3. Independent contribution of cognitive group on depressive syndromes

Table 3 shows the results of multiple regression analyses for the independent contributions of the cognitive group to each depressive syndrome. In model 1, MCI and AD were associated with increased risks of MiDD (OR = 1.83 for MCI and 2.17 for AD) and NIMH-dAD (OR = 1.59 for MCI and 2.11 for AD). In model 2, MCI and AD increased the risks of MiDD (OR = 1.78 for MCI and 2.42 for AD) and NIMH-dAD (OR = 1.56 for MCI and 2.24 for AD). In model 3, the results were similar to previous two models. In contrast, the risk of MaDD was not associated with cognitive group in all three models.

Table 3. Independent contribution of AD and MCI to depressive syndromes

Variables	MaDD			MiDD			NIMH-dAD					
	OR	95% CI	Wald	p	OR	95% CI	Wald	p	OR	95% CI	Wald	p
Model 1												
NC	Reference group				Reference group				Reference group			
MCI	0.65	0.32-1.29	1.54	0.215	1.83	1.10-3.05	5.49	0.019	1.59	1.07-2.35	5.29	0.021
AD	0.83	0.40-1.71	0.27	0.605	2.17	1.27-3.69	8.12	0.004	2.11	1.39-3.19	12.34	<0.001
Model 2												
NC	Reference group				Reference group				Reference group			
MCI	0.65	0.32-1.29	1.54	0.215	1.78	1.07-2.97	4.91	0.027	1.56	1.05-2.32	4.91	0.027
AD	0.83	0.40-1.72	0.26	0.607	2.42	1.41-4.14	10.31	0.001	2.24	1.47-3.41	14.20	<0.001
Model 3												
NC	Reference group				Reference group				Reference group			
MCI	0.70	0.35-1.41	1.00	0.318	1.80	1.08-3.01	5.02	0.025	1.63	1.10-2.43	5.79	0.016
AD	0.94	0.44-2.00	0.03	0.876	2.45	1.42-4.23	10.39	0.001	2.39	1.56-3.67	16.02	<0.001

Note: The results of multiple logistic regression models are presented with wald values. Model 1 included age, gender, years of education as covariates. Model 2 included VRS as a covariate in addition to those of model 1. Model 3 included the number of past MDE as a covariate in addition to those of model 2.

Abbreviations: MaDD, major depressive disorder; MiDD, minor depressive disorder; NIMH-dAD, National Institute of Mental Health provisional criteria for depression in AD; OR, odds ratio; CI, confidence interval; NC, no cognitive impairment; MCI, mild cognitive impairment; AD, Alzheimer's disease dementia; VRS, vascular risk score; MDE, major depressive episode

4. Sensitivity analysis

The results of the subgroup analyses were very similar to those for the whole study population. Table 4 shows the frequency of depressive syndromes and the severity of depression in the subgroup of patients who did not use any psychotropic medication. While the frequencies of MaDD did not show any significant difference among cognitive groups ($\chi^2 = 0.26, p = 0.609$), those of NIMH-dAD showed significant group differences ($\chi^2 = 7.14, p = 0.008$), with a gradual increase from NC to AD, and those of MiDD showed similar trend ($\chi^2 = 3.42, p = 0.064$). Among the subjects who did not use any psychotropic medication, no one reported 2 or more past MDEs, and the frequencies of past MDE decreased gradually from NC to AD. The mean scores of GDS gradual increased from NC to AD ($F = 5.83, p = 0.003$), while those of HRSD did not show any difference between groups ($F = 2.03, p = 0.132$).

Table 5 shows the results of multiple regression analyses for the independent contributions of the cognitive groups to each

depressive syndrome in the subgroup. AD was associated with increased risk of MiDD in model 2 and 3, while similar but marginally significant association was observed in model 1. AD also increased the risk of NIMH-dAD in all three models. As for MCI, there was only a marginal association between cognitive group and the risks of milder syndromes. There was a trend for similar association between MCI and both milder depressive syndromes. In contrast, the risk of MaDD was not associated with MCI and AD in all three models.

Table 4. Frequency of depressive syndromes and severity of depression in subgroups without any use of psychotropic medication ($n = 679$)

Groups	NC ($n = 144$)	MCI ($n = 330$)	AD ($n = 205$)	F or χ^2	p
Frequency, N (%)					
MaDD	4 (2.8)	8 (2.4)	4 (2.0)	0.26	0.609
MiDD	13 (9.0)	52 (15.8)	34 (16.6)	3.42	0.064
NIMH-dAD	25 (17.4)	85 (25.8)	62 (30.2)	7.14	0.008
Number of past MDE, N (%)					
0	131 (91.0)	309 (93.6)	201 (98.0)		
1	13 (9.0)	21 (6.4)	4 (2.0)		
≥ 2	0 (0)	0 (0)	0 (0)		
Depression Scale					
HRSD [0-68]	3.2 (4.3)	3.8 (4.2)	4.1 (3.8)	2.03	0.132
GDS [0-30]	9.8 (6.7)	11.4 (6.8)	12.3 (6.7)	5.83	0.003†

Note: Data for categorical variables are presented as N (%) and analyzed through linear by linear association with the χ^2 values presented in the table.

Abbreviations: NC, no cognitive impairment; MCI, mild cognitive impairment; AD, Alzheimer's disease dementia; NIMH-dAD, National Institute of Mental Health provisional criteria for depression in AD; MaDD, major depressive disorder; MiDD, minor depressive disorder; MDE, major depressive episode; HRSD, Hamilton Rating Scale for depression; GDS, Geriatric Depression Scale

Table 5. Independent contribution of AD and MCI to depressive syndromes in subgroups without any use of psychotropic medication (*n* = 679)

Variables	MaDD				MiDD				NIMH-dAD			
	OR	95% CI	Wald	<i>p</i>	OR	95% CI	Wald	<i>p</i>	OR	95% CI	Wald	<i>p</i>
Model 1												
NC	Reference group				Reference group				Reference group			
MCI	0.84	0.24-2.94	0.07	0.788	1.76	0.91-3.39	2.86	0.091	1.53	0.92-2.55	2.64	0.104
AD	0.69	0.16-2.95	0.25	0.619	1.88	0.94-3.79	3.14	0.077	1.93	1.12-3.34	5.60	0.018
Model 2												
NC	Reference group				Reference group				Reference group			
MCI	0.82	0.23-2.87	0.10	0.752	1.74	0.90-3.38	2.71	0.100	1.52	0.91-2.55	2.59	0.108
AD	0.81	0.19-3.52	0.08	0.779	2.25	1.10-4.60	4.99	0.026	2.11	1.21-3.67	6.95	0.008
Model 3												
NC	Reference group				Reference group				Reference group			
MCI	0.86	0.25-3.02	0.06	0.814	1.76	0.91-3.42	2.81	0.093	1.54	0.92-2.56	2.73	0.098
AD	0.92	0.21-4.02	0.01	0.907	2.31	1.13-4.73	5.23	0.022	2.17	1.24-3.78	7.35	0.007

Note: The results of multiple logistic regression models are presented with wald values. Model 1 included age, gender, years of education as covariates. Model 2 included VRS as a covariate in addition to those of model 1. Model 3 included the number of past MDE as a covariate in addition to those of model 2.

Abbreviations: MaDD, major depressive disorder; MiDD, minor depressive disorder; NIMH-dAD, National Institute of Mental Health provisional criteria for depression in AD; OR, odds ratio; CI, confidence interval; NC, no cognitive impairment; MCI, mild cognitive impairment; AD, Alzheimer's disease dementia; VRS, vascular risk score; MDE, major depressive episode

IV. Discussion

To our knowledge, this is the first reported study to investigate the frequency of various depressive syndromes defined by formal diagnostic criteria in the elderly across a broad cognitive continuum, from NC to MCI and AD, in the same setting. As expected, the results revealed that the frequencies of MaDD remained constant regardless of cognitive decline, whereas those of MiDD and NIMH-dAD were much higher and increased gradually as cognitive impairment progressed.

Previous studies reported the prevalence of MaDD to be 1–4% in a normal elderly population (30, 31), 3.4–19.6% in MCI (12, 13), and 1–35% in AD (2, 4, 7, 8, 11). The frequency of MiDD was reported to be 4–13% in a normal elderly population (31, 32), 17–27% in MCI (12, 13), and 22–27% in AD (4, 8, 10). Taken together, there seems to be an increasing trend in the occurrence of each depressive syndrome, from normal aging to MCI and AD. However, it was difficult to confirm any trend because of considerable

differences in study settings, recruitment strategies, and assessment methods between studies. With regard to NIMH-dAD, no previous study has reported the frequency in normal elderly and MCI populations, while it was reported that 30–45% of AD patients met the syndrome criteria (8, 9). To overcome this limitation, we examined the frequency of these depressive syndromes in the elderly with NC, MCI, and AD from the same setting using the same methodologies.

The frequency of MaDD in this study was quite constant, at approximately 5%, regardless of cognitive status. Even after controlling for the influence of demographic variables, vascular risks, and the number of past MDE, cognitive diagnostic groups, which probably reflect the degree of Alzheimer's disease progression, were not associated with MaDD frequency. These findings suggest that MaDD may not be influenced by Alzheimer's disease process.

In contrast to MaDD, milder depressive conditions, such as MiDD and NIMH-dAD, were more common in individuals with poorer

cognitive function: 10.2% in NC, 17.8% in MCI, and 20.3% in AD for MiDD and 20.4% in NC, 29.7% in MCI, and 35.8% in AD for NIMH-dAD. Multiple logistic regression analyses also revealed that cognitive diagnostic group had independent positive associations with the frequency of MiDD and NIMH-dAD. Overall, all these findings indicate that Alzheimer's disease associated brain injury probably increase the occurrence of the milder form of depressive syndrome. These results were similar to previous reports on the prevalence or incidence of depressive symptoms in a variety of neurodegenerative conditions. From the findings from the Cache county study, dementia patients showed a higher rate of depressive symptoms in comparison with non-demented subjects, regardless of the type of dementia (33). Previous studies also reported that cerebrovascular risk factors were associated with incident depressive symptoms and syndromes (34-36). Putting these phenomena together, Lavretsky et al. proposed the concept of clinically significant non-major depression (CSNMD) and insisted that CSNMD is usually associated with medical conditions, including neurodegenerative changes in the elderly brain.

Of the two non-major depressive syndromes, the prevalence of NIMH-dAD was much higher than that of MiDD in all cognitive subgroups. This difference can be explained by the characteristics of the diagnostic criteria. Although criteria for MiDD require only two to four depressive symptoms, the symptoms must be present for 2 weeks. In contrast, the criteria for NIMH-dAD require a similar number of depressive symptoms without any additional terms regarding the symptom period. Criteria for NIMH-dAD also include additional depressive symptoms that are common in AD patients: irritability and social isolation. In other words, the criteria for NIMH-dAD are more inclusive and specific to depression in AD in comparison with those of MiDD, and this may explain higher frequency of NIMH-dAD.

This study has a couple of limitations. First, as the subjects were recruited from a university memory clinic population, the frequency of depressive syndromes obtained in the current study cannot be generalized to estimate the prevalence of those syndromes in community populations due to selection bias. Second, approximately 34.9% of the subjects of this study were taking antidepressants or

other psychotropic medications at the time of assessment, and this might change the depression severity in those individuals and distort the results of our study. However, when we reanalyzed for a subgroup of patients who did not use any psychotropic medication, the association patterns between each depressive syndrome and cognitive diagnostic group were quite similar which supported our findings for the whole study population.

In conclusion, the current findings obtained from a large number of cognitively diverse elderly individuals indicated that milder depressive syndromes (i.e., MiDD or NIMH-dAD) are highly prevalent in general and more common in individuals with MCI and AD, conditions, while the frequency of severe depression (i.e., MaDD) is much lower and not related to cognitive impairment. Our results of the differential associations of various depressive syndromes with the cognitive impairment groups suggested that milder form of depression is influenced by Alzheimer-related neurodegenerative process, while severe form of depressive syndrome is not associated with such process.

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국문초록

서론: 본 연구에서는 치매 클리닉의 비인지장애 (no cognitive impairment, 이하 NC), 경도인지장애 (mild cognitive impairment, 이하 MCI), 그리고 알츠하이머성 치매 (Alzheimer's disease dementia, 이하 AD) 군에서 다양한 우울 증후군의 빈도를 조사하였으며, 그 결과를 바탕으로 인지 집단이 심각한 우울 증후군과 상대적으로 경한 우울 증후군의 빈도에 미치는 영향에 차이가 존재하는지 분석을 통하여 알아보았다.

방법: 216명의 NC, 478명의 MCI, 316명의 AD 대상자들이 본 연구에 포함되었다. 우울 증후군은 정신장애 진단 및 통계 편람 제4판의 주요우울장애 (major depressive disorder, 이하 MaDD) 및 경도우울장애 (minor depressive disorder, 이하 MiDD), 그리고 미국 국립정신보건연구소에서 잠정적으로 제안한 알츠하이머병에서의 우울 증후군 (National Institute on Mental Health provisional diagnostic criteria for depression in AD, 이하 NIMH-dAD)으로 정의하였으며, 각 우울증후군의 빈도를 조사하였다.

결과: 전체 대상자에서 MaDD 빈도는 5.4%, MiDD 빈도는 16.9%, 그리고 NIMH-dAD 빈도는 29.6%로 조사되었다. 각 인지 집단에서의 빈도를 살펴보면, MaDD 빈도는 NC군에서 6.9%, MCI군에서 4.6%, 그리고 AD군에서 5.7%로 조사되었다. MiDD 빈도는 NC군에서 10.2%, MCI군에서 17.8%, 그리고 AD군에서 20.3%였다. NIMH-dAD는 각 군에서 20.4%, 29.7%, 그리고 35.8%의 빈도를 보였다. MaDD 빈도가 인지 집단에 다른 차이를 보이지 않은 반면, 상대적으로 경한 우울 증후군인 MiDD 그리고 NIMH-dAD는 통계적으로 유의미한 차이를 보였으며, NC군에서 AD군으로 갈수록 서서히 빈도가 증가하였다.

결론: 본 연구에서는 다양한 우울 증후군과 인지 장애 군간의 관계를 살펴보았으며, 그 결과는 상대적으로 경한 우울 증후군은 알츠하이머병 관련 신경퇴행성 변화의 밀접한 영향을 받는 반면에 심각한 우울 증후군은 그러한 영향을 받지 않는다는 것을 시사하였다.