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Depression in Vascular Dementia Is Quantitatively and Qualitatively Different from Depression in Alzheimer's Disease

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Key Words
Major depressive disorder · Minor depressive disorder · Vascular dementia · Alzheimer's disease

Abstract
Background/Aims: To compare the prevalence and characteristics of depression in vascular dementia (VaD) and Alzheimer's disease (AD) after adjusting for dementia severity and gender. ***Methods:*** One hundred and eight pairs of VaD and AD patients matched for dementia severity and gender were assessed. ***Results:*** Major depressive disorder (MDD) was more prevalent in the VaD group than in the AD group (20.4% in VaD, 10.2% in AD, p = 0.04, Cochran-Mantel-Haenszel, CMH, test) regardless of the dementia severity and gender. The odds ratio for developing MDD in the VaD group versus the AD group was estimated to be 2.20 (95% confidence interval = 1.02–4.74). Neurovegetative symptoms such as 'felt tired and weak all the time' (30.6% in VaD, 13.9% in AD, p = 0.003, CMH test) and 'changed weight without trying' (16.7% in VaD, 6.5% in AD, p = 0.02, CMH test) were more prevalent in the VaD group than in the AD group. ***Conclusion:*** Depression in VaD was quantitatively and qualitatively different from that in AD regardless of the severity of dementia and gender; depression was more prevalent, severer and more retarded and vegetative in VaD than in AD.

Introduction

Depression commonly accompanies vascular dementia (VaD) and Alzheimer's disease (AD). Depression in dementia is clinically important because it is a significant but treatable determinant of morbidity and caregiver distress [1, 2]. According to the populations surveyed, the assessment methodologies employed and the diagnostic criteria applied, the prevalence rate of major depressive disorder (MDD) varies widely and has been reported to be 19–45% in VaD patients [3, 4] and 8–20% in AD patients [3–6].

In AD, depression may be caused by neurodegenerative changes in brain regions that are involved in mood regulation. AD patients with depression were found to show neurodegenerative changes in brainstem aminergic nuclei with relative preservation of basal forebrain cholinergic neurons that innervate the hippocampi and neocortices [7–10]. On the other hand, the involvement of

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white matter and subcortical gray matter may account for the genesis of depression in VaD. Subcortical pathologies in the forms of leukoaraiosis, Binswanger's disease or lacunar states are present in the majority of VaD patients and may be the sole finding in 40% of VaD patients [11, 12]. Although no consensus has been reached on the relationship between depression and cerebral lesion location [13], damage to striatopallidothalamocortical pathways may play an important role in the development of depression via altering the serotonergic and adrenergic circuits [14].

However, it has been debated whether depression in VaD is clinically distinct from that in AD. Although depression has been reported to be more prevalent, severer and more vegetative in VaD than in AD in several studies [4, 15–18], it was not replicated in other studies [19–22]. Furthermore, dementia severity and gender were not considered in these studies. Since the prevalence and characteristics of depression are known to vary according to the severity of dementia, comparisons of depression in VaD and AD should be made on the basis of dementia severity. The genders of the VaD and AD subjects should also be considered since gender is a well-known risk factor for depression [23–25].

Therefore, we compared the prevalence and characteristics of depression in VaD and AD after matching subjects for dementia severity and gender to examine whether depressions in VaD and AD are quantitatively and qualitatively different.

Materials and Methods

Subjects were recruited from two dementia clinics (Seoul National University Hospital, Seoul National University Bundang Hospital) and memory screening programs offered to community residents in Seoul and Seongnam, Korea. The subjects were the first visitors for the evaluation of dementia and had not suffered from major psychiatric illnesses on axis I including MDD, bipolar disorder and schizophrenia before cognitive decline. The subjects had not taken or were not taking antidementia medications and antidepressants. All the subjects were Koreans.

All the subjects were administered a standardized clinical interview, physical and neurological examinations, and laboratory tests including either the brain CT or MRI according to the protocol of the Korean version of the CERAD assessment battery (CERAD-K) [26]. The modified Hachinski ischemic score [27] is included in CERAD-K.

Subsequently, all available information was reviewed by a panel of 4 experienced dementia research neuropsychiatrists for the determination of the Clinical Dementia Rating (CDR) index and diagnosis. Two of the research neuropsychiatrists were certified CDR raters at the Memory and Aging Project of Alzheimer's Disease Research Center, Washington University School of Medicine. Dementia was defined according to the DSM-IV diagnostic criteria [28]. VaD was diagnosed according to the National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria [29], and AD was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria [30]. Only probable VaD patients and probable AD patients were enrolled. The CDR indices and genders of VaD and AD patients were tightly matched.

Depressive symptoms were evaluated using the Depressive Symptom Checklist included in the CERAD-K. MDD was diagnosed according to the DSM-IV criteria and minor depressive disorder (MnDD) according to research criteria proposed in appendix B of the DSM-IV criteria. Subjects in whom MDD preceded cognitive decline were excluded.

Demographic characteristics and the measures that were continuous in nature were analyzed using analysis of variance, and the frequencies of depressive disorders and symptoms were compared using the Cochran-Mantel-Haenszel (CMH) test. No adjustments of the p value criterion were made for multiple comparisons, since the goal of the study was to explore differences between the two diagnostic groups and reduce the likelihood of the type II errors as well as type I error. The odds ratios (OR) for developing depressive disorders and symptoms in VaD versus AD were estimated using the Mantel-Haenszel test, and the homogeneity of OR was tested using the Breslow-Day (BD) test. All the statistical analyses were performed using SPSS version 11.0.

Table 1. Demographic characteristics of VaD and AD patients

	VaD (n = 108)	AD (n = 108)
Age, years	71.45 ± 7.37	72.37 ± 8.61
Sex, % female	50.90	50.90
Education, years	6.67 ± 5.24	6.86 ± 5.29
Blessed dementia scale	4.53 ± 3.29	3.00 ± 2.87
Sum of boxes score of CDR	6.34 ± 4.18	6.55 ± 4.66
Modified Hachinski ischemic score	7.61 ± 2.95*	0.65 ± 1.23
MMSE	17.24 ± 5.43*	14.88 ± 6.50

* $p < 0.01$, Student t test. MMSE = Mini Mental State Examination.

Results

One hundred and eight probable VaD patients and 108 gender- and CDR-matched AD patients were enrolled (table 1). The proportion of women was 50.9%. Mean ages (71.45 ± 7.37 years in VaD patients, 72.37 ± 8.61 years in AD patients) and levels of education (6.67 ± 5.24

Table 2. Frequencies of MDD and MnDD in the VaD and AD patients

	MDD[1]		MnDD	
	VaD (n = 108)	AD (n = 108)	VaD (n = 108)	AD (n = 108)
Severity of dementia				
Very mild (CDR = 0.5, n = 78)	8 (20.5)	4 (10.3)	7 (17.9)	6 (15.4)
Mild (CDR = 1, n = 84)	10 (23.8)	4 (9.5)	7 (16.7)	7 (16.7)
Moderate (CDR = 2, n = 30)	3 (20.0)	2 (13.3)	2 (13.3)	4 (26.7)
Severe (CDR = 3, n = 24)	1 (8.3)	1 (8.3)	1 (8.3)	0
Gender				
Female (n = 110)	16 (14.5)	5 (4.5)	12 (10.9)	9 (8.2)
Male (n = 106)	6 (5.7)	6 (5.7)	5 (4.7)	8 (7.5)
Total (n = 216)	22 (20.4)	11 (10.2)	17 (15.7)	17 (15.7)

Figures in parentheses are percentages.
[1] $\chi^2 = 4.45$, p = 0.04, CMH test adjusting for severity of dementia and gender.

years in VaD patients, 6.86 ± 5.29 years in AD patients) were similar in the two groups ($p > 0.1$, Student t test).

The proportions of very mild (CDR = 0.5), mild (CDR = 1), moderate (CDR = 2) and severe (CDR ≥3) cases were 36.1% (n = 39), 38.9% (n = 42), 13.9% (n = 15) and 11.1% (n = 12), respectively. Sum of boxes score of CDR (6.34 ± 4.18 in VaD patients, 6.55 ± 4.66 in AD patients, $p > 0.1$ by Student t test) and Blessed Dementia Scale scores (4.53 ± 3.29 in VaD patients, 3.00 ± 2.87 in AD patients, $p > 0.1$ by Student t test) were similar in the two groups indicating that global severities and activities of daily living impairments were quite comparable.

However, the VaD group had a higher mean Mini Mental State Examination (MMSE) score than the AD group (17.24 ± 5.43 in the VaD group, 14.88 ± 6.50 in the AD group, p = 0.004 by Student t test), indicating that the global cognition of VaD patients was probably better than that of the AD patients at a given CDR index. As expected, the VaD group had a higher mean modified Hachinski ischemic score than the AD group ($p < 0.001$ by Student t test; table 1).

Table 2 shows the frequencies of MDD and MnDD in the VaD and AD groups. MDD was more prevalent in the VaD group (20.4% in the VaD group, 10.2% in the AD group, p = 0.04, CMH test). The Mantel-Haenszel common OR for developing MDD in the VaD group versus the AD group was estimated to be 2.20 (95% confidence interval, CI = 1.02–4.74) using the CMH test (p = 0.04). The OR for developing MDD in the VaD group versus the AD group did not differ by the severity of dementia and gender (p = 0.1, BD test). Although the OR for developing MDD were greater in women (OR = 4.10, 95% CI = 1.38–12.18) than in men (OR = 1.00, 95% CI = 0.30–3.33), the differences did not reach statistical significance (p = 0.08, BD test). In contrast to MDD, MnDD was not more prevalent in the VaD group (15.7%) than in the AD group (15.7%) regardless of the dementia severity and gender ($p > 0.1$, CMH test). The frequencies of MDD and MnDD tended to fall abruptly in the severe cases (CDR = 3) in both VaD and AD groups, although the differences did not reach statistical significance ($p > 0.1$, χ^2 test).

Table 3 shows the frequencies of individual depressive symptoms. 'Lost interest in things that used to be pleasurable' was the most prevalent symptom in both VaD and AD groups (37.0% in the VaD group, 25.9% in the AD group). In the VaD group, 'felt tired and weak all the time' (30.6%) and 'had to be moving all the time (agitation) and/or felt slowed down' (27.8%) were the next most prevalent symptoms, whereas in the AD group, 'had to be moving all the time (agitation) and/or felt slowed down' (18.5%) and 'changed eating habits' (15.7%) were the next most prevalent symptoms.

All depressive symptoms tended to be more prevalent in the VaD group than in the AD group. The mean numbers of depressive symptoms were 2.19 ± 2.64 in the VaD group and 1.30 ± 2.01 in the AD group (p = 0.006, Student t test). Of the 9 depressive symptoms, 'changed weight without trying' (16.7% in the VaD group, 6.5% in the AD group, p = 0.02, CMH test) and 'felt tired and weak all the time' (30.6% in the VaD group, 13.9% in the AD group, p = 0.003, CMH test) were about 3 times more prevalent in the VaD group than in the AD group regardless of demen-

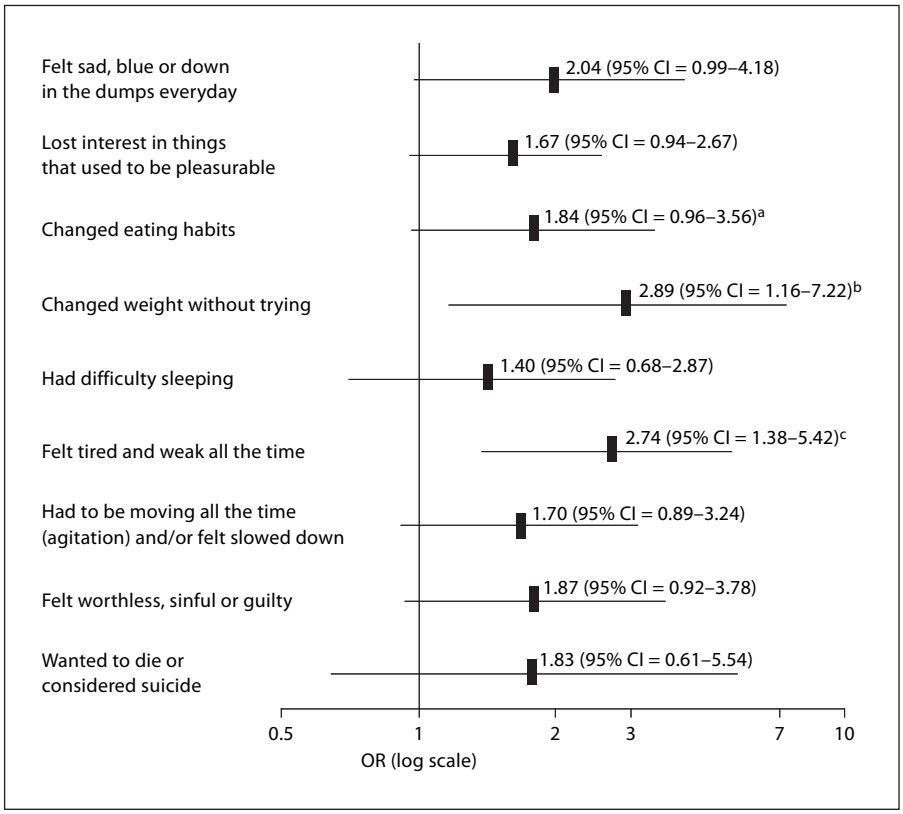

Fig. 1. The OR and 95% CI for depressive symptoms in VaD versus AD. The OR were assessed by Mantel-Haenszel common OR estimates adjusting for the severity of dementia and gender. [a] $p = 0.01$, BD test; [b] $p < 0.05$, [c] $p < 0.01$, CMH test.

Table 3. Frequencies of depressive symptoms in the VaD and AD patients

	VaD (n = 108)	AD (n = 108)
Felt sad, blue or down in the dumps everyday	25 (23.1)	14 (13.0)
Lost interest in things that used to be pleasurable	40 (37.0)	28 (25.9)
Changed eating habits	28 (25.9)	17 (15.7)
Changed weight without trying	18 (16.7)	7 (6.5)
Had difficulty sleeping	21 (19.4)	16 (14.8)
Felt tired and weak all the time	33 (30.6)	15 (13.9)
Had to be moving all the time (agitation) and/or felt slowed down	30 (27.8)	20 (18.5)
Felt worthless, sinful or guilty	25 (23.1)	15 (13.9)
Wanted to die or considered suicide	9 (8.3)	5 (4.6)

Figures in parentheses are percentages.

tia severity and gender ($p > 0.1$, BD tests). Differences in the frequencies of 'changed eating habits' were significant only in the female patients with mild disease ($p = 0.01$, BD test). The frequencies of 'changed eating habits' were 55.5 and 7.4% in the female patients with mild VaD and AD, respectively (OR = 15.63, 95% CI = 3.07–79.59). The differences in the frequencies of the other 6 symptoms were not statistically significant ($p > 0.05$, CMH test; fig. 1).

Discussion

As has been previously reported [6, 17], depressive disorders were quite common in both VaD (36.1%) and AD patients (25.9%) in the present study. In the Canadian Study of Health and Aging, dementia patients were found to be more likely to exhibit depression than those without dementia (OR = 2.4; 95% CI = 0.9–3.1) [31]. The preva-

lences of MDD in our VaD (20.4%) and AD (10.2%) groups were higher than the previously reported prevalence of MDD in nondemented Korean elderly subjects (7.5%) [32] and the weighted average prevalence in community-dwelling older adults (1.8%) [33]. The prevalence of MnDD was also higher in the VaD (15.7%) and AD (15.7%) groups than its weighted average prevalence in community-dwelling older adults (9.8%) [33], although the differences were not as large as those of MDD.

In our sample, VaD patients showed a higher frequency of MDD than the AD patients matched for dementia severity and gender, which is consistent with earlier observations that VaD patients are more likely to have MDD than AD patients [3, 4, 6, 16, 34–37]. However, the OR for developing MDD in VaD patients versus AD patients varied widely in the previous studies (OR = 1.7–8.2). Cooper and Mungas [37] estimated the prevalence rate of depression in 810 AD and 502 VaD patients selected from the California Alzheimer's Disease Diagnostic and Treatment Center Program and found an OR of 1.7. In the two studies of Ballard et al. [4, 6], the OR were 4.0 (95% CI = 1.4–11.3) and 2.8 (95% CI = 1.1–7.0). Newman [35] reported that the prevalence rate of MDD was 3.2% for AD and 21.3% for VaD, giving a crude OR of 8.2 (95% CI = 1.7–40.2) in a population sample. In our sample, those were 2.20 (95% CI = 1.02–4.74), which is lower than most of those reported previously [4, 6, 34, 36]. Furthermore, the overrepresentation of MDD in VaD has not been consistently replicated [19–22]. Along with the different diagnostic criteria used, different populations sampled and the different instruments applied, the differences in the severity of dementia and gender within and between the VaD and AD groups might have contributed to the wide variability in reported OR [4, 6, 34, 36, 37] and conflicting results [19–22], at least in part.

Our study has an advantage over other previous studies in this context because we tightly matched 108 pairs of subjects (one with VaD and one with AD) with respect to gender and CDR. When comparing depression in the different types of dementia, severity of dementia and gender should be matched for the following reasons. First, the prevalence of depression changes with the progression of dementia [4, 17, 18], and the severity of dementia may vary according to the types of samples (clinical samples, community samples or institutionalized patients) [38, 39]. Second, nearly twice as many women as men develop depression, and women often have different symptoms. Furthermore, while VaD is slightly more prevalent among men than women [40], AD is much more prevalent among women [41, 42].

Although MMSE scores were used to match the severity of dementia in a number of previous studies [4, 16], we used the CDR index instead of MMSE scores in matching the global severity of dementia because MMSE with its emphasis on language and memory often inadequately grades the severity of VaD patients [43]. In our sample, the VaD group had a higher MMSE score than the AD group at a given CDR, which indicates that the severity of global cognition may not necessarily coincide with the severity of dementia. If we had used MMSE instead of CDR to match VaD and AD patients, the VaD group would have probably been deemed to have contained severer cases than the AD group. This may confound the relation between the type of dementia and depression since the frequencies of these depressive disorders (MDD, MnDD) tended to fall abruptly in severe VaD and AD, as shown by our sample and by previous studies [44, 45]. Difficulty in assessing depression in severe dementia patients may have contributed to a decrease in the prevalence of depression in both VaD and AD patients. In terms of pathophysiology, the progression of the central cholinergic deficit may limit the development of major depressive episodes in severe stages in AD [8, 46], whereas this has been little studied in VaD.

Our study also demonstrated that depression is severer in VaD than in AD when the severities of dementia and gender are similar. Mean numbers of depressive symptoms were significantly higher in the VaD group, and MDD was more prevalent than MnDD (15.7%) in the VaD group but less prevalent in the AD group. These confirm the earlier observations using unmatched patients [47] or MMSE-matched patients [16].

Compared with the depression in AD, psychomotor symptoms like loss of energy and vegetative symptoms like weight loss and loss of appetite have been reported to be more prevalent in depression co-occurring with VaD [16, 19, 48]. In our sample, the neurovegetative symptoms ('felt tired and weak all the time', 'changed weight without trying', 'changed eating habits') were more common in VaD patients than in AD patients, which further supports earlier observations. Although it is not clear yet why the depression is more retarded and vegetative in VaD than in AD, different depressogenic mechanisms may account for the different depressive symptom profile between VaD and AD. Whereas AD patients show the preferential involvement of more posterior cortical regions that may not play a critical role in the expression of depression, VaD patients are more likely to exhibit striatopallidothalamocortical pathway damage which may influence motivation and psychomotor speed [11, 12, 14].

In addition, some vegetative symptoms in VaD patients may stem from comorbid conditions other than depression. For example, weight loss in VaD patients may stem from the profiles of depressive symptoms or from other medical conditions such as immobilization and difficulties with food intake.

In conclusion, regardless of the severity of dementia and gender, depression was found to be more frequent, severer, more retarded and vegetative in VaD than in AD.

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