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Behavioral and psychological symptoms in Korean patients with mild Alzheimer's disease: Preliminary study

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Abstract

Behavioral and psychological symptoms of dementia are major components of Alzheimer's disease. In this study, we aimed at investigating the prevalence and severity of behavioral and psychological symptoms of dementia in very mild to mild Alzheimer's disease. Forty-four patients with Alzheimer's disease who visited the neurology outpatient clinic of Seoul Medical Center were included. A trained neurologist or a supervised test technician administered the neuropsychological test, the Seoul Neuropsychological Screening Battery including Mini Mental State Examination and Clinical Dementia Rating. The instrument used for assessing behavioral and psychological symptoms of dementia was Neuropsychiatric Inventory-Questionnaire. In order of prevalence, apathy, depression, irritability, anxiety, and agitation were the most common symptoms occurring in very mild-to-mild Alzheimer's disease group. The prevalence and severity of behavioral and psychological symptoms of dementia were found to be in positive correlation with the Clinical Dementia Rating scores. Behavioral and psychological symptoms of dementia are found even in the very early stage of Alzheimer's disease, apathy and depression being the most common symptoms. Physicians should be aware of this when managing dementia patients.

INTRODUCTION

Dementia is a syndrome that shows decline in both cognitive function and non-cognitive function, which are represented by memory decline and behavioral and psychological symptoms). The prevalence of dementia is on the rise with the ageing population.[1,2] The non-cognitive symptoms are termed Behavioral and Psychological Symptoms of Dementia (BPSD), suggested by the International Psychogeriatric Association (IPA).[3] The common symptoms include anxiety, irritability, wandering, aggression, shouting, restlessness, hallucination, delusion, depression, sexual disinhibition, eating problem and sleep-wake disturbances.[4] The non-cognitive symptoms have been regarded as mere accompanying symptoms of cognitive dysfunction, and overlooked by the clinicians due to its lack of diagnostic significance.[5] However, BPSD have been gaining more attention as major problems in AD patients, because of the high incidence which range from 25% to 80%, and their impact on the patient's quality of life.[6-8] Additionally, BPSD are associated with caregiver distress and increased likelihood of institutionalization, raising the total medical cost.[6,9] Therefore, proper acknowledgement and management of BPSD is very important in treating demented patients, as well as maintaining cognitive function. BPSD are reported to be positively correlated with the severity of dementia, in patients who are institutionalized.[10] Most of the previous studies regarding BPSD have been focusing on patients who are institutionalized, and have advanced AD.[10-12] In this study, we sought to evaluate the severity and kinds of BPSD in newly diagnosed dementia patients on an outpatient protocol.

METHODS

We enrolled patients who came to the Seoul Medical Center neurology department on an outpatient protocol, between the age of 60 and 85, and newly diagnosed with Alzheimer's dementia. Patients were included if they met the criteria of probable AD from Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) was fulfilled.[13,14] For more comprehensive and detailed assessment of

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cognition, Seoul Neuropsychological Screening Battery (SNSB) was used.[15] SNSB consists of K-MMSE test, attention tests (Digit span), lingual and relevant tests (Korean-Boston Naming Test, K-BNT), visuospatial test (Rey Complex Figure Test, RCFT), memory function items (Seoul Verbal Learning Test, SVLT), frontal/ executive function items (Controlled Oral Word Test, COWAT; Korean-Color Word Stroop Test, K-CWST), Geriatric Depression Scale (GDS), Barthel Activities of Daily Living (B-ADL), and Clinical Dementia Rating Scale (CDR). We narrowed the population to those who have very mild or mild AD, with CDR score of 0.5 or 1, who were ambulatory and had caregivers who could accompany them to the hospital. We excluded the ones with history of alcohol abuse, substance abuse, who were treated for psychiatric illness and had medical illness that could aggravate cognitive dysfunction.

Neuropsychiatric Inventory (NPI)

A clinician conducted a Neuropsychiatric Inventory (NPI) scale, a brief clinical instrument for evaluating psychopathology in dementia.(16) NPI evaluates following symptoms: delusion; hallucination; agitation/ aggression; depression/ dysphonia; anxiety; elation/euphoria; apathy/ indifference; disinhibition; irritability/ lability; aberrant motor behavior; sleep/ night-time behavior; appetite/ eating disorder. The prevalence of each symptom and the severity were assessed on the basis of questionnaire administered to the caregiver, and average scores were drawn. The severity was numeralized according to the answer; none (score=0), mild (score=1), moderate (score=2), severe (score=3). Statistical analysis was done using the SPSS (version 11.5). All p-values were two-tailed and statistical significance was accepted for p-values<0.05. Data are expressed as mean ± standard deviations (S.D.). The means and S.D. of the values were calculated and submitted to statistical analysis by Fisher's exact test and Wilcoxon rank sum test.

RESULTS

Total of 44 AD patients were included. 23 patients had very mild AD, with CDR score of 0.5, and the other 21 had mild AD, with CDR of 1. In mild AD group, compared to the very mild AD group, ADL score was significantly low. There was no significant difference in sex, age, duration of education, K-MMSE score and GDS score. (Table 1)

Upon detailed cognitive assessment, the patients with CDR 1 showed significantly lower scores in the RCFT (Rey Complex Figure Test) copy score, the animal part of COWAT (Controlled Oral Word Association Test) and the K-CWST (Korean-Color Word Stroop Test) compared to the patients with CDR 0.5 (Table 2). However, the scores of K-BNT (Korean-Boston naming Test) and Verbal and Visual memory test did not show any significant differences.

As a whole group, the most common symptoms were apathy/ indifference depression/ dysphoria, irritability/ lability, anxiety, agitation/aggression, in order of prevalence. (Table 3) The prevalence was slightly different with the subgroup analysis. In the CDR 0.5 group, apathy/ indifference, depression/ dysphoria, irritability/ lability were the most common, followed by agitation/aggression and appetite/eating disorder. In the other group, the order of prevalence was the same as that of

Table 1: Demographic and clinical characteristics of patients with Alzheimer's disease

	Total (n=44)	CDR 0.5 (n=23)	CDR 1 (n=21)
Sex (Male:Female)	14:30	8:15	6:15
Age (years)	76.4±7.0	76.2±7.2	76.6±6.9
Education (years)	5.6±5.4	5.5±5.0	5.6±5.9
K-MMSE	18.0±10.3	18.3±5.9	17.7±13.7
CDR	0.7±0.3	0.5	1
GDS	17.7±8.5	18.2±8.5	17.2±8.6
ADL	17.8±3.9	19.5±1.2	15.9±5.0*

Values are presented as mean±standard deviation. (*p<0.05)
CDR, Clinical Dementia Rating Scale; GDS, Geriatric Depression Scale; ADL, Activities of Daily Living

Table 2: Neuropsychological profiles of the two Alzheimer's disease groups

	CDR 0.5	CDR 1	*p* value
Digit span			
Forward	4.1±1.2	3.7±1.2	0.590
Backward	2.8±1.0	2±1.0	0.089
K-BNT	29.7±11.2	26.7±10.0	0.428
RCFT copy score	18.1±11.9	8.3±9.4	0.024*
Verbal memory (SVLT)			
Immediate recall total	10.4±4.4	9.2±3.7	0.386
Delayed recall	0.6±1.1	0.7±1.2	0.869
Visual memory (RCFT)			
Immediate recall total	3±4.3	1.9±3.6	0.799
Delayed recall	3±4.6	0.9±2.9	0.178
COWAT			
Animal	7.3±2.3	5.4±3.6	0.036*
Market	7.3±3.0	6.3±3.9	0.149
Phonemic total	6.1±5.1	4±6.0	0.210
K-CWST color reading	35.5±24.5	13.4±16.3	0.001*

Values are presented as mean±standard deviation (*p<0.05).
CDR, Clinical Dementia Rating Scale; K-BNT, Korean-Boston Naming Test; RCFT, Rey Complex Figure Test; COWAT, Controlled Oral Word Association Test; K-CWST, Korean-Color Word Stroop Test.

the whole group. Regardless of the groups, apathy/indifference were the most frequent BPSD, and there was no statistically significant difference of the variables between two groups. That is, the sorts of neuropsychiatric symptoms and the incidence of them are alike in very mild and mild stages of AD, suggesting that the abnormal behaviors start to develop even in the very early stages of the disease. Despite no significant difference, the rate of BPSD in CDR 1 group was higher, and the symptoms were more severe than the other group. (Figure 1).

DISCUSSION

The results of this study showed that BPSD are fairly common in very mild-to-mild Alzheimer's dementia. Notably, even in patients with CDR 0.5, the prevalence was not significantly different from patients with CDR 1. The most frequent symptoms were apathy/indifference, and the prevalence of the symptoms was 60% in the CDR 0.5 group and 71% in the CDR 1 group. The second most common symptoms were depression/dysphoria and the prevalence was 52% in CDR 0.5 group and 66% in the other group. In addition to apathy/indifference and depression/ dysphoria, irritability/lability was frequently observed, and this is in line with previous literatures.[11,17] The frequency and incidence of neuropsychiatric symptoms rise with progression of disease. However, the fact that the prevalence does not vary significantly from very mild stage to mild stage implies that the symptoms might begin in the very early stage of the disease. It is important for clinicians to detect them and start treatment as soon as possible.

There was a previous report assessing the neuropsychiatric symptoms of AD, but the study included patients of more advanced stage, mean CDR of 1.7, so the prevalence of BPSD in the very early stage of AD has not been assessed properly.[11] Interestingly, in the same report, the prevalence of hallucination, anxiety, appetite/eating disorder appeared to be lower than our study, which included patients with mean CDR of 0.7 (4.6% vs 9.1%, 11.3% vs 22.73, 0% vs 15.91%, respectively). In another report, which included large number of patients with Alzheimer's disease, vascular dementia, and diffuse lewy body dementia and assessed incidence and characteristics of neuropsychiatric symptoms, the mean CDR was 2.1. This, again, reflects that researches have been mainly concentrated on abnormal behaviors of the advanced dementia patients.[12]

This study suggests that various BPSD, as well as the cognitive dysfunction such as memory

Table 3: Neuropsychiatric inventory of the patients with Alzheimer's disease according to Clinical Dementia Rating Scale (CDR) severity

Behavioral variables	Prevalence {n(%)}				Severity (0-3)			
	Total (n=44)	CDR 0.5 (n=23)	CDR 1 (n=21)	P value (CDR 0.5 vs 1)	Total	CDR 0.5	CDR 1	P value (CDR 0.5 vs 1)
Delusion	3 (6.82)	1 (4.35)	2 (9.52)	0.599	0.11±0.44	0.04±0.21	0.19±0.60	0.468
Hallucination	4 (9.09)	1 (4.35)	3 (14.29)	0.335	0.11±0.39	0.04±0.21	0.19±0.51	0.248
Agitation/ Aggression	9 (20.45)	5 (21.74)	4 (19.05)	1.000	0.30±0.67	0.30±0.70	0.29±0.64	0.880
Depression/ Dysphoria	26 (59.09)	12 (52.17)	14 (66.67)	0.373	1.05±1.10	0.87±1.01	1.24±1.18	0.287
Anxiety	10 (22.73)	3 (13.04)	7 (33.33)	0.155	0.41±0.84	0.26±0.75	0.57±0.93	0.132
Elation/ Euphoria	3 (6.82)	1 (4.35)	2 (9.52)	0.599	0.07±0.26	0.04±0.21	0.10±0.30	0.501
Apathy/ Indifference	29 (65.91)	14 (60.87)	15 (71.42)	0.535	1.43±1.25	1.30±1.22	1.57±1.29	0.434
Disinhibition	3 (6.82)	1 (4.35)	2 (9.52)	0.599	0.14±0.55	0.13±0.63	0.14±0.48	0.536
Irritability/ Lability	17 (38.64)	8 (34.78)	9 (42.86)	0.758	0.68±1.03	0.52±0.90	0.86±1.15	0.396
Aberrant motor behavior	2 (4.55)	0 (0)	2 (9.52)	0.222	0.11±0.54	0	0.24±0.77	0.134
Sleep/Night-time behavior	2 (4.55)		1 (4.76)	1.000	0.07±0.33	0.04±0.21	0.10±0.44	0.922
Appetite/ Eating disorder	7 (15.91)	5 (21.74)	2 (9.52)	0.416	0.18±0.45	0.26±0.54	0.10±0.30	0.256

Values are presented as mean±standard deviation (*p<0.05).

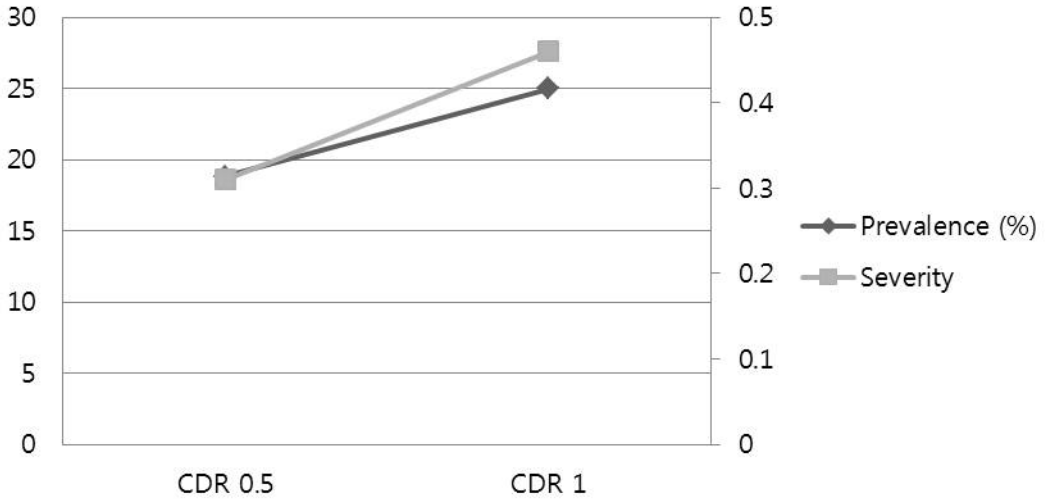

Figure 1. Behavioral and Psychological Symptoms of Dementia (BPSD) prevalence and severity according to CDR, Clinical Dementia Rating Scale (CDR).

decline, can develop in even very early stages of Alzheimer's. Several studies have reported that BPSD such as agitation, depression, apathy and irritability impair the patient's quality of life. Also, symptoms such as delusion, agitation/aggression, anxiety, irritability/ lability, depression/ dysphoria are reported to aggravate caregiver's distress. Thus, comprehensive understanding and proper management of the BPSD are necessary.[18,19]

The pathogenesis of BPSD remains unclear and under-investigated, because its multi-factorial nature makes specific localization very difficult.[20] However, several studies have been conducted, elucidating the localizing value of BPSD. Mega *et al*. reported that frequency of apathy increased with dementia severity; 42% in mild cognitive impairment, 80% in moderate cognitive impairment, and 92% in severe cognitive impairment. The report implies that pathological progression of the disease and presentation of apathy seems to be in close relationship with each other. In two reports, single-photon emission computed tomography (SPECT) showed hypoperfusion in anterior cingulate area in patients with apathy. [21,22] Hirono *et al*. reported that AD patients with depression showed decreased glucose metabolism in frontal lobe compared to those who did not have depression.[23] Also, neuropathologic study of the patients with AD and depression showed more cell loss in locus ceruleus than those without depression.[24] In study of agression, the degree of rostral locus ceruleus cell loss and cholinergic deficit were highly correlated with aggressive behavior.[25,26] In this study, there was no significant difference of prevalence and severity of neuropsychiatirc symptoms between the two groups, but there was a trend toward increase in severity. The results of our study, that CDR 1 group showed significantly lower scores in frontal assessment test (COWAT and K-CWST), is in line with previous literature, that neuronal loss in frontal lobe and frontal lobe function is associated with progression of the disease and aggravation of BPSD.

The mainstay of BPSD treatment is pharmacological approach. Anti-psychotic drugs have been widely used, and addition of anti-depressants, anti-anxiolytics, anti-convulsants and acetylcholine esterase inhibitors according to the clinical feature is recommended.[27] Researches on non-pharmacological measures are in progress. When environmental change seems responsible for the aggravation of BPSD, making environmental manipulations to simplify and enhance the surrounding is suggested.[28] Also, physical stimuli, exercise and music are reported to be useful for reducing anxiety and restlessness.[29,30] Additionally, despite no proven efficacy, psychosocial treatment, reminiscence treatment and light therapy are being tried.[27,31,32] Although pharmacological treatment is the most effective treatment of BPSD, considering the poor response to medication of some symptoms such as wandering, interfering behavior, repetitive questioning, and limitations due to adverse events of the drugs, investigation of new therapeutic strategies along with careful examination of the clinical feature should be ensued.[33]

Unlike previous studies that included patients with advanced dementia, this study focused on patients who were newly diagnosed from the outpatient protocol. Rather high prevalence shown in our study calls for clinician's attention to BPSD from the early stage. The limitations, such as small population, low statistical power, oversimplified BPSD variables, and lack of data on caregiver's distress should be supplemented by future studies.

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DISCLOSURE

Conflict of interest: None

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