Research Article:

Effects of neuropsychiatric symptoms of dementia on reductions in activities of daily living in patients with Alzheimer's disease

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Running title: Effects of NPS on ADL

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Abstract

Aim: In patients with Alzheimer's disease (AD), cognitive impairments cause a progressive reduction in activities of daily living (ADL). Neuropsychiatric symptoms (NPS) also appear in most patients; however, the association between NPS and reductions in ADL remains unclear. The present study evaluated whether NPS influence such reductions using two different ADL measures in patients with AD.

Methods: Among 546 consecutive outpatients who visited the memory clinic at the Jikei University Kashiwa Hospital, we recruited 208 AD patients and investigated the correlations between either the Physical Self-Maintenance Scale (PSMS) score or the instrumental ADL (IADL) level and each of the Behavioral Pathology in Alzheimer's Disease (Behave-AD) subscales. To clarify the causal relationships of these correlations, we then verified the associations between statistically significant demographic variables and the Behave-AD subscales as well as the two ADL scales (PSMS score and IADL percentage) using a general linear model.

Results: Neither the PSMS nor the IADL results were significantly influenced by the aberrant motor behaviors score. However, the IADL was significantly influenced by the Mini-Mental State Examination (MMSE) score. Furthermore, diurnal rhythm disturbances and the interaction between diurnal rhythm disturbances score and the MMSE score significantly influenced the PSMS results.

Conclusion: Basic ADL reductions may be influenced by diurnal rhythm disturbances in addition to cognitive impairments in patients with AD. Furthermore, the interaction between the diurnal rhythm disturbances score and cognitive function may also influence basic ADL.

Keywords: activities of daily living (ADL), Alzheimer's disease, executive function, neuropsychiatric symptoms (NPS)

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease characterized by cognitive impairments (e.g., memory disorder, visuospatial disorder, attentional deficit and executive dysfunction) as its core symptoms; these symptoms directly impair activities of daily living (ADL), including self-care, housework, and social activities.[1,2,3] Among these cognitive impairments, visuospatial cognitive impairments, but not memory impairments, influence basic ADL (BADL) related to self-care (e.g., taking a bath, eating a meal, using the toilet, changing clothes).[4,5] Furthermore, executive dysfunctions crucially influence instrumental ADL (IADL: e.g., financial management, shopping, meal preparation, using transportation), including more complicated actions.[6,7] These two different types of ADL may be influenced by the effects of distinct cognitive functions; therefore, preserving the cognitive status during the disease course might lead to the maintenance of ADL.

As conventional marginal symptoms, neuropsychiatric symptoms (NPS) (e.g., psychosis, aggressiveness, depression, and aberrant motor behaviors) appear in most patients with AD, which in turn increases the mental and physical distress of their caregivers throughout the long-term disease course.[8,9] These NPS are thought to be caused by interactions among psychosocial, demographic, and biological factors as a suitable pathophysiological model.[10,11,12] Among the causative factors, the relationship between cognitive impairments (as a core symptom) and NPS (as a marginal symptom) has been described in previous studies. Especially, delusion, aberrant behavior, and apathy are reportedly correlated with executive dysfunction, which consists of superior cognitive modalities reflecting frontal-subcortical circuits.[10,13,14]

Taken together, the cognitive deterioration in AD appears to cause ADL reductions directly and might influence NPS partially. Cross-sectionally, several previous studies have suggested that sub-symptoms of NPS (e.g., hallucinations, aberrant motor behaviors, diurnal disturbances, and anxiety) influenced the ADL status. However, these studies did not investigate the involvement of cognitive deterioration simultaneously.[15,16,17,18] How severe NPS and cognitive deterioration in AD influence the simultaneous reductions in ADL has not yet been studied using a single model. Thus, to clarify the effect of NPS on reductions in ADL, an investigation of interactions between cognitive status and the severities of NPS sub-symptoms is required. Additionally, some longitudinal studies have shown that a severer state of NPS at baseline predicted a faster progression in AD, implying that the severity of NPS affects the prognosis, including ADL reductions, throughout the course of AD.[18,19,20] We hypothesized that any distinct behavioral or psychological problems or cognitive deteriorations may affect BADL and/or IADL. Identifying the relevance of such effects may help to clarify the mechanism responsible for disturbed ADL and contribute to preventing the acceleration of ADL reductions caused by neurodegenerative progression.

In the present analysis, based on the hypothesis that the NPS accompanying cognitive impairment may influence ADL reductions, including IADL and basic self-maintenance functions, in AD patients, we examined the cross-sectional correlations among scores in each scale rating NPS severity, neuropsychological status, and ADL levels using the statistical coefficient of correlation. To elucidate the mechanisms by which NPS contribute to ADL reductions, we used cross-sectional data to clarify the relationships between NPS and ADL. Next, to elucidate the causal relationships of these correlations, we verified the associations between statistically significant variables of demographic factors and sub-symptoms of the NPS scale and two different ADL statuses (BADL and IADL) using a general linear model.

METHODS

Participants

Among the 546 consecutive ambulatory outpatients who visited the memory clinic at the Jikei University Kashiwa Hospital between August 2006 and December 2013, a total of 208 AD patients were recruited (76.0% female, 78.1±7.6 years old). The selected patients were diagnosed as having probable AD based on the National Institute of Neurological Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.[1] All the diagnoses were made after an examination of the patients' past medical history, an evaluation of physical or neurological examinations, routine blood tests, and magnetic resonance imaging (MRI) findings by a geriatric psychiatrist (one of authors). The duration of illness was defined as the time from the initial appearance of symptoms until consultation, as determined from information provided by reliable caregivers. Moreover, patients with severe physical disease, with movement disorders leading directly to ADL reductions, with a history of head trauma or brain damage, with a history of drug or alcohol abuse, or who were receiving psychotropic medication were excluded. The geriatric psychiatrists and clinical psychologist were experienced at performing neuropsychological and behavioral examinations, and the inter-rater validity of the scales was sustained by periodic discussions and exchanges of views. This study was approved by the Ethics Committee of the Jikei University School of Medicine and Kashiwa Hospital.

Assessments

We used the Mini-Mental State Examination (MMSE: score range from 0 to 30) to evaluate each patient's general cognitive status.[21] This neuropsychological test is easily administered at bedside within 10 to 15 minutes by a clinical psychologist. The geriatric psychiatrists used the Clinical Dementia Rating scale (global CDR; score range: 0-3) to assess the severity of each patient's dementia, and the results were: 0=normal [*n*=0], 0.5=questionable [*n*=28] 1=mild [*n*=123], 2=moderate [*n*=40], 3=severe [*n*=7], and unidentifiable [*n*=10].[22] To evaluate the severities of NPS based on a caregiver interview, the Behavioral Pathology in Alzheimer's Disease (Behave-AD; score range: 0-75) scale was used.[23] The Behave-AD consists of the following 7 subscale domains: paranoid and delusional ideation (score range: 0-21); hallucinations (score range: 0-15); aberrant motor behaviors (score range: 0-9); aggressiveness (score range: 0-9); diurnal rhythm disturbances (score range: 0-3); affective disturbances (score range: 0-6); and anxieties and phobias (score range: 0-12).[23] Moreover, to examine the individual ADL status, we used the following two scales.[24] One is the Lawton IADL scale, which consists of 5 questions (ability to use telephone, shopping, mode of transportation, responsibility for own medications, and ability to handle finances) for male; 3 additional questions (food preparation, housekeeping, and laundry) are included for female. Since the maximum IADL scores differ between female (score range: 0-8) and male (score range: 0-5), the present study used the IADL percentage (%), which was calculated as follows: IADL percentage (%) in male =(raw score)/5 points ×100 (%) ; IADL percentage (%) in female =(raw score)/8 points ×100 (%). We used IADL percentages to correct for the sex differences in the evaluation of domestic-specific life-style in the present study. Moreover, to assess their BADL, we used the Physical Self-Maintenance Scale (PSMS; score range: 0-6) score consisting of the following 6 questions: toilet, feeding, dressing, grooming, physical ambulation, and bathing.[24]

Statistical analysis

In the primary analysis, the correlations between each of the 4 demographic factors (age in years, duration in years, education years, MMSE score) and the ADL status (PSMS score or IADL percentage) were examined using the Spearman rank correlation coefficient. Also, the correlations between each of the 7 Behave-AD subscale scores (paranoid and delusional ideation, hallucinations, aberrant motor behaviors, aggressiveness, diurnal rhythm disturbances, affective disturbances, anxieties and phobias) and the ADL status were examined using the Spearman rank correlation coefficient.

As a secondary analysis, we used a general linear model (GLM) analysis to examine the contribution or interactions between significant Behave-AD subscales and other factors as independent variables of each ADL status (PSMS score or IADL percentage). In the GLM analysis, significant variables were treated as covariates, and the PSMS and IADL percentage scores were regarded as dependent variables.

In the primary analysis, when extracting important variables from the 4 variables or the 7 Behave-AD subscales, we considered that a *P* value <0.05/4 (=0.0125) or a *P* value <0.05/7 (≒0.007) were statistically significant according to the Bonferroni-correction. In the secondary analysis, a *P* value <0.05 was considered statistically significant. IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp.) was used for all the statistical analyses.

RESULTS

Patient characteristics (Table 1)

Table 1 depicts the detailed demographics of the 208 subjects enrolled in the present investigation. The detailed mean and standard deviations (SD) scores of the demographic characteristics are shown in the table.

Correlations between PSMS score or IADL percentage and patient demographic variables

Table 2a depicts the correlations between the PSMS score or the IADL percentage (%) and the patient demographic variables (age in years, duration in years, education years, and MMSE score) using the Spearman rank correlation coefficient (Table 2a). The PSMS score was positively correlated with the MMSE score (ρ=0.422; P<0.001) (Table 2a). As significant correlations, the IADL percentage was positively correlated with the MMSE (ρ=0.342; P<0.001) (Table 2a).

Correlations between PSMS or IADL percentage and Behave-AD subscale scores

Table 2b depicts the correlations between the PSMS score or the IADL percentage and each of the 7 Behave-AD subscale scores (paranoid and delusional ideation, hallucinations, aberrant motor behaviors, aggressiveness, diurnal rhythm disturbances, affective disturbances, and anxieties and phobias) using the Spearman rank correlation coefficient (Table 2b). As significant correlations, the PSMS score was negatively correlated with aberrant motor behaviors (AMB) (ρ=-0.290; P<0.001) and diurnal rhythm disturbances (DRD) (ρ=-0.323; P<0.001) (Table 2b). The IADL percentage was negatively correlated with AMB (ρ=-0.325; P<0.001) and DRD (ρ=-0.244; P=0.003) (Table 2b).

Association of PSMS score or IADL percentage (%) with Behave-AD subscales and MMSE score (as a covariance)

According to the primary analysis, 2 significant independent variables (AMB or DRD) among the Behave-AD subscales were selected for analysis in the next step. Table 3 depicts whether the GLM of the AMB scores and the MMSE score (as a covariance) contributed to the PSMS score or the IADL percentage. The models showed that neither the PSMS score nor the IADL percentage was significantly influenced by either the AMB score (former: F=1.477, P=0.202; latter: F=2.003, P=0.083) or the interactions between the AMB score and the MMSE score (former: F=1.751, P=0.128; latter: F=2.101, P=0.069). However, the IADL percentage was significantly influenced by the MMSE score (F=5.066, P=0.026). Table 4 depicts whether the GLM of the DRD scores and the MMSE score (as a covariance) contributed to the PSMS score or the IADL percentage. The models showed that the DRD or the interaction between the DRD score and the MMSE score significantly influenced the PSMS score (former: F=4.673, P=0.004; latter: F=3.062, P=0.03). However, the DRD or the interaction between the DRD and the MMSE score did not significantly influence the IADL percentage (former: F=1.323, P=0.27; latter: F=0.953, P=0.417).

DISCUSSION

The present cross-sectional study examined the effects of NPS features or other factors on ADL reductions. The results showed that neither the AMB nor the DRD significantly influenced the IADL percentage. IADL reductions were, however, influenced by cognitive impairment. In addition, the DRD or the interaction between the DRD score and the MMSE score significantly influenced the PSMS score.

Previous reports have investigated associations between various types of cognitive deterioration and ADL reductions in patients with AD; however, the effects of NPS on ADL reductions remain unclear.[4,5,6,7] In the present analysis, the DRD influenced BADL reductions (PSMS score). The results of the analysis in this study also showed that the severer DRD tended to be lower BADL levels in patients with lower MMSE scores (severer cognitive impairment). DRD included disturbances in awakening or the sleep cycle during the night.[23] A poor sleep at night can lead to further declines in activity levels or behavioral alterations during the day, potentially leading to an inability to perform basic daytime actions in some patients.[25] A significant association between the MMSE score and self-care ADL has been shown in previous studies.[4,5,16] The results of the present study, in which an interaction between the DRD score and the MMSE score was shown to influence the PSMS score, supports such previously reported results, and DRD directly influence basic self-care ADL. The MMSE score did not significantly contribute to basic self-care ADL, meaning that neurocognitive impairments that interacted with DRD were associated with basic self-care ADL in patients with AD. Moreover, an impairment in visuospatial cognition, but not memory, reportedly influences BADL, particularly tasks related to self-maintenance, and impairments in visuospatial cognition are often described beginning at an early stage of AD.[4,5,26] IADL includes abilities such as using a phone, shopping, transportation, taking one’s own medications, finances, food preparation, housekeeping, and laundry, which are more complicated actions requiring a higher ability than self-maintenance functions. IADL scores have been consistently associated with executive dysfunction, reflecting superior cognitive modalities compared with other cognitive domains (i.e., memory disorder, visuospatial disorder, or attention deficit).[6,7] We also investigated the associations between DRD severity (0-3 points) and each PSMS subscore (0 or 1 points for “toilet”, “feeding”, “dressing”, “grooming”, “physical ambulation”, and “bathing”) by making 2-group comparisons using the Mann-Whitney test (a *P* value <0.008 [≒0.05/6] was considered statistically significant according to the Bonferroni-correction). The results showed that the DRD score was significantly associated with the subscores for toilet ($P<0.001$), physical ambulation ($P<0.001$), and bathing ($P=0.002$). These BADLs were mainly performed during the nighttime and may have been disturbed by DRD. Thus, DRD may lead to nocturia, failure of excretion, unstable locomotion, and impairment of bathing.

AMB include the following neurobehavioral patterns: (1) wandering (e.g., away from home or caregiver), (2) inappropriate behaviors (e.g., storing and hiding objects in inappropriate places; throwing clothing in a waste basket or putting empty plates in the oven; inappropriate sexual behaviors such as inappropriate exposure), and (3) purposeless activity (e.g., opening and closing a pocketbook, packing and unpacking clothing, repeatedly putting on and removing clothing, insistently repeating demands or questions).[23] Troublesome behavioral patterns might disturb the retention of daily actions requiring higher abilities. In the primary analysis, there was a significant correlation between AMB and ADLs (PSMS score and IADL percentage). A previous study reported that a significant association was found between the impairment of IADL and aberrant motor activity.[27] We speculated that this significant correlation might reflect ADL reductions influencing AMB among some NPS in patients with AD.

The MMSE total score reflects the global cognitive function with weighting for orientation and memory.[21] While some previous studies have reported that IADL disturbances were significantly correlated with AMB,[15,16,17] the present GLM analysis showed that IADL reductions might be influenced by only cognitive function, and not NPS. In the presently reported GLM, cognitive impairments, rather than AMB as serious NPS, tended to have a more robust influence on the IADL. Future studies should investigate the mechanisms of the disturbances of more complicated actions by serious NPS and their interactions with neurocognitive impairments.

The present study had some limitations, such as the relatively small sample size. As a reason, patients with psychotropic medication were excluded in this study. There may be cases in which psychotropic medication influences ADL because of adverse effects (e.g., diurnal somnolence, falls, and cognitive declines). In such cases it is difficult to identify which psychotropic medication or NPS influences the patient's ADL, and that is why we excluded patients on psychotropic medication from the present study. As another reason, the general physical status influencing ADL during the daytime was not strictly assessed in the present study; however, since only ambulatory subjects were able to visit the hospital and be enrolled in the study, this restriction was regarded as an indicator of a common index of health in the present investigation. Moreover, since we enrolled only ambulatory outpatients, our cohort included many subjects with mild or moderate AD. Secondly, the Behave-AD was used as an assessment scale evaluating NPS severity, but this scale does not include "apathy" among its neuropsychiatric sub-symptoms. Apathy in AD is correlated with ADL reductions and cognitive impairment.[10,18] Thirdly, we could not have enough information about the living style of the patients. (e.g., they live alone, they live with family, or they live in the facility). Fourthly, we used the IADL percentage to emphasize that the IADL scale differs between males (5 points) and females (8 points), since men rarely do housework in traditional Japanese families. Finally, while we hypothesized that NPS caused a functional decline, the reverse cause and effect, in which a functional decline causes severe NPS, could instead exist. To resolve this issue, a longitudinal investigation may be required. However, cognitive function in patients with AD can decline or otherwise change during the long-term disease course, complicating the relationship. Therefore, we used cross-sectional data to clarify the relationship between NPS and ADL.

Despite these limitations, the present study suggests that ADL reductions may be influenced by NPS in addition to cognitive impairments as core symptoms in AD. Therefore, to prevent ADL reductions, careful attention to DRD is needed. Furthermore, clarifying the mechanisms of neurobehavioral effects on disturbed ADL (self-maintenance function and IADL) may provide important information regarding the selection of treatment stages that might reduce the early burden placed on caregivers, thereby preventing the acceleration of ADL reductions during the course of disease progression.

DISCLOSURE STATEMENT

The authors declare no conflicts of interest.

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Table 1. Demographics of patients with AD (*n*=208)

Variables (score range)	Mean±SD or number
Age, in years	78.1±7.6
Sex (Female/Male)	158/50
Main caregiver (spouse/child/other/unidentifiable)	71/128/7/2
Education years	11.7±5.1
Duration, in years	3.2±2.4
MMSE scores (0-30)	18.5±4.6
CDR score (0/0.5/1/2/3/unidentifiable)	0/28/123/40/7/10
Behave-AD total scores (0-75)	6.9±5.9
Paranoid and delusional ideation[1)] (0-21)	1.2±2.2
Hallucinations[1)] (0-15)	0.1±0.5
Aberrant motor behaviors [1)] (0-9)	1.2±1.3
Aggressiveness[1)] (0-9)	1.1±1.7
Diurnal rhythm disturbances[1)] (0-3)	0.4±0.7
Affective disturbances[1)] (0-6)	0.8±1.2
Anxieties and phobias[1)] (0-12)	1.5±1.3
IADL score (Female: 0-8; Male: 0-5)	4.4±2.2
IADL percentage (%)	62.2±28.6
PSMS score (0-6)	5.1±1.5

Abbreviations:
AD: Alzheimer's Disease,
Behave-AD: Behavioral Pathology in Alzheimer's Disease Rating Scale
CDR: Clinical Dementia Rating
IADL: Instrumental Activities of Daily Living
MMSE: Mini Mental State Examination, PSMS: Physical Self—Maintenance Scale
SD: standard deviation
[1)]Behave-AD subscale score

Table 2a). Correlations between PSMS score or IADL percentage (%) and patient characteristics

	Age, in years	Duration, in years	Education years	MMSE score
PSMS score	ρ=-0.116 (P=0.163)	ρ=-0.149 (P=0.072)	ρ=0.096 (P=0.253)	**ρ=0.422***¶ (P<0.001)**
IADL percentage (%)	ρ=-0.108 (P=0.193)	ρ=-0.200* (P=0.016)	ρ=0.091 (P=0.277)	**ρ=0.342***¶ (P<0.001)**

ρ: Spearman correlation coefficients. *P<0.05, **P<0.01, ***P<0.001,
¶P<0.0125=0.05/4 (Bonferroni correction)
Values in bold type are significant results after Bonferroni correction.

Table 2b). Correlations between PSMS score or IADL percentage (%) and Behave-AD subscale scores

Behave-AD subscale scores	Paranoid and delusional ideation	Hallucinations	Aberrant motor behaviors	Aggressiveness	Diurnal rhythm disturbances	Affective disturbances	Anxieties and phobias
PSMS score	ρ= -0.063 (P=0.449)	ρ= -0.113 (P=0.174)	**ρ= -0.290***¶ (P<0.001)**	ρ= -0.057 (P=0.494)	**ρ= -0.323***¶ (P<0.001)**	ρ= 0.012 (P=0.882)	ρ= 0.096 (P=0.251)
IADL percentage (%)	ρ= -0.153 (P=0.067)	ρ= -0.135 (P=0.106)	**ρ= -0.325***¶ (P<0.001)**	ρ= -0.056 (P=0.507)	**ρ= -0.244**¶ (P=0.003)**	ρ= 0.024 (P=0.775)	ρ= 0.155 (P=0.063)

ρ: Spearman correlation coefficients. **P<0.01, ***P<0.001, ¶ P<0.007≒0.05/7 (Bonferroni correction)
Values in bold type are significant results after Bonferroni correction.

Table 3. Association of (a) PSMS score and (b) IADL percentage (%) with aberrant motor behaviors (AMB) and MMSE score

Statistical comparison	*df*	*F* score	*P* value
(a) AMB score	5	1.477	0.202
MMSE score	1	0.736	0.392
AMB score × MMSE score	5	1.751	0.128
(b) AMB score	5	2.003	0.083
MMSE score	**1**	**5.066**	**0.026***
AMB score × MMSE score	5	2.101	0.069

R^2=0.308. Generalized linear models were used to investigate whether the AMB score and the MMSE score were associated with the PSMS score.
**P*<0.05, R^2=0.249. Generalized linear models were used to investigate whether the AMB score and the MMSE score were associated with IADL (%).
Abbreviations: AMB: Aberrant motor behaviors, IADL: Instrumental Activities of Daily Living,
PSMS: Physical Self-Maintenance Scale, MMSE: Mini-Mental State Examination

Table 4. Association of (a) PSMS score and (b) IADL percentage (%) with diurnal rhythm disturbances (DRD) and MMSE score

Statistical comparison	*df*	*F* score	*P* value
(a) **DRD score**	**3**	**4.673**	**0.004****
MMSE score	1	0.458	0.5
DRD score × MMSE score	**3**	**3.062**	**0.030***
(b) DRD score	3	1.323	0.27
MMSE score	1	0.009	0.924
DRD score × MMSE score	3	0.953	0.417

R^2=0.304. Generalized linear models were used to investigate whether the DRD score and the MMSE score were associated with the PSMS score.
*P<0.05, **P<0.01, R^2=0.191. Generalized linear models were used to investigate whether the DRD score and the MMSE score were associated with IADL (%).
Abbreviations: DRD: Diurnal rhythm disturbances, IADL: Instrumental Activities of Daily Living,
PSMS: Physical Self-Maintenance Scale, MMSE: Mini-Mental State Examination