Focus on Alzheimer's Disease and Related Disorders

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Gender Differences in Clinical Manifestations and Outcomes Among Hospitalized Patients With Behavioral and Psychological Symptoms of Dementia

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ABSTRACT

Objective: To clarify whether hospitalized patients with behavioral and psychological symptoms of dementia (BPSD) show gender differences in manifested symptoms and outcomes.

Method: A chart review study of patients hospitalized from April 2006 to March 2008 for the treatment of BPSD was conducted. We evaluated the prevalence of symptoms in each of 7 clusters constituting a subscale of the Behavioral Pathology in Alzheimer's Disease Rating Scale and the incidence of favorable discharge, defined as discharge to the patient's own home or care facility. Dementia was diagnosed according to DSM-IV.

Results: The study cohort comprised 122 men and 170 women. The men were more likely than the women to present with aggressiveness (78% vs 52%, P < .001) and diurnal rhythm disturbances (89% vs 79%, P < .05) and less likely to present with paranoid, delusional ideation (12% vs 41%, P < .001); hallucination (7% vs 29%, P < .001); affective disturbances (20% vs 40%, P < .001); and anxieties and phobias (15% vs 44%, P < .001). Incidence of favorable discharge was lower in the men (58% vs 77%, P = .001). Even after matching for age, sociodemographic factors, and physical and cognitive functions, the differences in these symptoms persisted, with the exception of diurnal rhythm disturbances. Incidence of favorable discharge was lower in the men (60% vs 77%, P = .0173).

Conclusion: The data demonstrated gender differences in BPSD and outcomes among hospitalized patients. The findings should be considered when deciding on the optimal management plan for patients with BPSD.

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Improvements in nutrition, medicine, and hygiene have enabled increased life spans worldwide. However, higher rates of longevity in large populations have raised the serious problem of a steep increase in the prevalence of dementia.^{1,2} This phenomenon is likely to produce an enormous social burden in the future that could threaten the financial stability of government systems.³

Japan has the highest life expectancy of any country in the world⁴ and is already tackling an impending surge of dementia. The Japanese government launched the Long-Term Care Insurance strategy^{5,6} in 2000 and is increasingly establishing care systems and facilities to support people with dementia in their own communities and outside the hospital system. This approach aims not only to improve patient quality of life, but also to reduce medical expenditure. However, despite such efforts, numbers of hospitalized patients with dementia in psychiatric facilities continue to rise, primarily due to worsening behavioral and psychological symptoms of dementia (BPSD). A nursing home study⁷ revealed

- Men hospitalized for treatment of BPSD were more likely than women to present with aggressiveness and less likely to present with paranoid, delusional ideation; hallucination; affective disturbances; and anxieties and phobias.
- Men with BPSD were less likely than women to be discharged into their communities.
- More effective treatment options for aggressiveness and enhanced care strategies may be required for men.

that 90% of demented people manifest BPSD, and because such symptoms are frustrating and disruptive, family members or nursing home staff often have difficulty in dealing with BPSD even in cooperation with the outpatient services offered by psychiatric hospitals. Thus, many patients require hospitalization. In 2008, more than 50,000 patients with dementia spent some time in a psychiatric hospital in Japan.⁸ The goal of inpatient treatment is to return patients to their own home or a care facility as soon as possible. However, prolonged hospital stays additively precipitate increases in the number of hospitalized people with dementia, which is predicted to reach 100,000 in Japan by 2026.⁸

Recent studies in nursing homes and outpatient settings have addressed the importance of gender difference in BPSD and disease course in patients with dementia.^{9–20} Some studies^{13–18} of dementia patients have found that men are more likely to exhibit aggressive behaviors, while other reports cite an increased risk of mortality among male patients compared to female patients.^{19,20} However, similar studies in hospitalized patient populations are scarce.^{21,22}

The present study sought to clarify the role of gender in the prevalence of manifested symptoms and in outcomes among patients hospitalized for BPSD treatment.

METHOD

The medical records of patients who were hospitalized in the acute psychogeriatric ward of our institution were reviewed by a single psychiatrist. The institutional review board approved this retrospective analysis and waived the requirement for written informed consent.

Patients

Consecutive patients who had been admitted to the acute psychogeriatric ward of Ishikawa Prefectural Takamatsu Hospital (Kahoku City, Japan) for the treatment of BPSD from April 2006 to March 2008 were enrolled in this study. All patients had severe BPSD such that they could not be cared for in their own home or care facilities or be treated in outpatient settings. Patients with severe comorbid physical disease were judged to be ineligible for hospitalization in the acute psychogeriatric ward in order to prioritize medical treatment of those physical comorbidities. Patients with a record of past hospitalizations in our acute psychogeriatric ward and those who had behavioral symptoms prior to their cognitive decline or psychiatric comorbidities were excluded from the study.

Measures

In all patients, the following items were evaluated and recorded within a week after admission according to the institutional protocol.

Demography. Data including age, gender, living situation including residency and family style before hospitalization, and relationship with caregiver were recorded based on an interview or psychiatry social worker-administered questionnaire to the family members or staff of the care facility or hospital. Residency before hospitalization was classified as the patient's own home, a group home, a care facility, or a medical hospital. A group home is a care facility peculiar to Japan in which a group of people spend their daily lives basically on their own, with staff for support only when needed. Family style refers to the people with whom the patients had lived. For patients who had lived with family members other than their partner or in care facilities, group homes, or medical hospitals, family style was classified as "other." The relationship of the caregiver to the patient was classified as partner, son or daughter, other family member or relative, or staff.

Reasons for hospitalization. Behavioral problems causing distress for the caregiver, which had become the primary reason for hospitalization, were recorded based on the caregiver interview. Reasons for hospitalization were classified into combative behavior, overactivity, and apathy or depression. Combative behavior comprised physically or verbally aggressive behaviors during or between care provisions, such as hitting, kicking, biting, throwing things, cursing, and screaming. Overactivity included behaviors that were nonaggressive but required constant monitoring, such as wandering aimlessly, trying to reach a different place, exhibiting restlessness, or performing repetitious mannerisms. Apathy and depression included serious apathetic or depressive behavior such as severe appetite loss, refusal to eat, refusal of medication, or suicidal tendencies.

Type of dementia. Diagnosis of dementia was made by either of the 2 experienced geriatric psychiatrists (T.K. and M.K.) according to *DSM-IV*, based on the interview with patients and family members or staff, physical and neurologic findings, laboratory data, and brain imaging.

Behavioral and psychiatric symptoms. Prevalence of behavioral and psychiatric symptoms was evaluated by the 2 study geriatric psychiatrists (T.K. and M.K.) using the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD).²³ Presence or absence of symptoms in each of the following 7 clusters constituting a subscale of BEHAVE-AD was recorded: paranoid and delusional ideation, hallucinations, aggressiveness, activity disturbances, diurnal rhythm disturbances, affective disturbances, and anxieties or phobias.

Table 1. Demographic Characteristics of Hospitalized Patients With Behavio	ral
and Psychological Symptoms of Dementia, Before and After Matching	

	Before	Matching ^a	After Matching ^b	
	Men	Women	Men	Women
Demographic Characteristic	(n = 122)	(n = 170)	(n = 100)	(n = 100)
Age, mean (SD), y	79 (7.0)	82 (6.9)***	79 (7.0)	80 (5.9)
Type of dementia, n (%)				
Alzheimer's disease	73 (60)	112 (66)	66 (66)	61 (61)
Vascular dementia	25 (20)	9 (5)***	11 (11)	15 (15)
Others	24 (20)	49 (29)	23 (23)	24 (24)
Residency before hospitalization, n (%)				
Own home	76 (62)	113 (66)	60 (60)	69 (69)
Group home	10 (8)	23 (14)	10 (10)	6 (6)
Care facility	11 (9)	18 (11)	11 (11)	7(7)
Medical hospital	25 (20)	16 (9)*	19 (19)	18 (18)
Family style, n (%)				
Alone	20 (16)	45 (27)	19 (19)	12 (12)
With partner only	37 (30)	18 (11)***	26 (26)	24 (24)
Other	65 (53)	107 (62)	55 (55)	64 (64)
Caregiver's relationship to patient, n (%)				
Partner	65 (53)	13 (8)***	46 (46)	48 (48)
Son or daughter	18 (15)	79 (46)***	16 (16)	25 (25)
Other family member or relative	11 (9)	31 (18)	11 (11)	10 (10)
Staff	28 (23)	47 (28)	27 (27)	17 (17)
MMSE score, mean (SD)	7.0 (7.4)	10.0 (8.3)**	7.5 (7.5)	6.6 (6.3)
N-ADL scale score, mean (SD)	23.5 (12.8)	28.7 (12.7)***	24.4 (12.7)	25.7 (11.9)

^aDichotomous and continuous characteristics were compared using the χ^2 test and *t* test, respectively.

^bDichotomous and continuous characteristics were compared using the multinomial logistic regression analysis or McNemar test and the Wilcoxon signed rank test, respectively.

Abbroxistic

Abbreviations: MMSE = Mini-Mental State Examination, N-ADL = Nishimura's A	ctivities of
Daily Living.	

Cognitive function. Cognitive functions were measured by the geriatric psychiatrists in the acute psychogeriatric ward using the Mini-Mental State Examination (MMSE).²⁴

Functional state of daily living. Activities of daily living were scored by well-trained nursing staff according to the Nishimura's Activities of Daily Living (N-ADL) scale,²⁵ which is one of the most utilized scales for the evaluation of activities of daily living in Japan. In the N-ADL scale, 5 items are evaluated: walking/sitting, range of activities, dressing/ bathing, eating, and excretion. Each item is scored from 0 to 10 points, and the total (maximum score is 50) is regarded as the N-ADL score. The reliability of the scale when completed by nursing staff has been reported to be good.²⁵

Intervention

Patients received pharmacologic intervention as clinically indicated. All patients were treated under the supervision of the aforementioned 2 geriatric psychiatrists based on clinical judgments. There was no limit to the time allowed in the acute psychogeriatric ward.

Statistical Analysis

The primary endpoint of this study was the prevalence of each BEHAVE-AD cluster at the time of hospital admission. The secondary endpoints included incidence of favorable discharge and time to favorable discharge. *Favorable discharge* refers to moving the patient to his/her own home, the group home, or other care facility. This rating was otherwise classified as *unfavorable discharge*, which included death during hospitalization and transfer to the medical hospital due to deterioration of physical conditions.

All statistical analyses were performed using Stata statistical software (version 11.0; Stata Corp LP; College Station, Texas).

In descriptive statistics before matching, *t* tests were used to test the differences between men and women in age, MMSE score, and N-ADL score. The χ^2 test was used for frequency.

The 2 groups (men vs women) were also compared after matching for factors that may affect the patient's living situation or cognitive or physical state to enable a proper comparison of prevalence for each cluster of BPSD. We used propensity score matching methods to produce matched pairs comprising the gender groups. To estimate the propensity scores, age, residency before hospitalization, family style, relationship with caregiver, MMSE score, N-ADL score, and type of dementia were used as covariates of exposure (being male) in a logistic regression model. Propensity score estimation and matching were performed using

the Stata PSMATCH2 program. For each causal contrast specified, men were matched to women on estimated propensity scores using the nearest-neighbor approach²⁶ within calipers of 0.02. After matching on propensity scores, the Wilcoxon signed rank test was used for age, MMSE score, and N-ADL score, and a multinomial logistic regression analysis or McNemar test was used to analyze frequencies. A log-rank test was used to test the differences in time to favorable discharge. Unfavorable discharge or hospitalization at the study end was treated as censor. Statistical significance was defined as a 2-tailed *P* value of <.05. The Bonferroni correction was used to adjust *P* values for multiple comparisons.

RESULTS

A total of 292 patients were identified as eligible for this study. The demographic characteristics before matching for all patients are detailed in Table 1. Age was lower and prevalence of vascular dementia was greater in the men than in the women. The men also stayed more frequently in medical hospitals before hospitalization. Men were more likely to live with their partner only, and the caregiver was more frequently their partner and less frequently their son or daughter. Regarding cognitive and physical function, both MMSE scores and N-ADL scores were lower in men than in women. Reasons for hospitalization and behavioral and psychiatric symptoms presented at the time of admission

^{*}P < .05.

^{**}P<.01. ***P<.001.

Table 2. Clinical Manifestations of Behavioral and Psychological Symptoms of Dementia in Hospitalized Patients, Before and After Matching

	Before Matching ^a		After Matching ^b	
	Men	Women	Men	Women
Clinical Manifestation	(n=122)	(n = 170)	(n = 100)	(n = 100)
Reasons for hospitalization, n (%)				
Combative behavior	57 (47)	40 (24)***	44 (44)	18 (18)***
Overactivity	52 (43)	92 (54)	44 (44)	69 (69)**
Apathy or depression	13 (10)	38 (22)*	12 (12)	13 (13)
Behavioral and psychological symptoms, n (%)				
Paranoid and delusional ideation	15 (12)	70 (41)***	15 (15)	34 (34)**
Hallucinations	8 (7)	49 (29)***	6 (6)	30 (30)***
Aggressiveness	95 (78)	88 (52)***	75 (75)	63 (63)*
Activity disturbances	119 (98)	159 (94)	97 (97)	97 (97)
Diurnal rhythm disturbances	108 (89)	134 (79)*	87 (87)	93 (93)
Affective disturbances	24 (20)	68 (40)***	19 (19)	40 (40)**
Anxieties and phobias	18 (15)	74 (44)***	12 (12)	34 (34)***

^aDichotomous characteristics were compared using the χ^2 test.

^bDichotomous characteristics were compared using the multinomial logistic regression analysis or the McNemar test.

*P<.05.

**P<.01.

***P<.001.

Table 3. Psychotropic Medications Used in Hospitalized Patients With Behavioral and Psychological Symptoms of Dementia, Before and After Matching

	Before Matching ^a		After Matching ^b	
	Men	Women	Men	Women
Medication Use	(n = 122)	(n = 170)	(n = 100)	(n = 100)
Before admission				
Use of antipsychotics, n (%) Dose of antipsychotics, ^c mean (SD), mg/kg Use of cholinesterase inhibitor, n (%)	60 (49) 3.0 (2.6) 22 (18)	81 (48) 2.7 (2.3) 51 (30)*	51 (51) 3.0 (2.7) 19 (19)	52 (52) 3.1 (3.3) 32 (32)*
After admission				
Use of antipsychotics, n (%) Dose of antipsychotics, ^d mean (SD), mg/kg Use of cholinesterase inhibitor, n (%)	101 (83) 4.7 (4.2) 38 (31)	139 (82) 4.2 (4.2) 82 (48)**	81 (81) 4.8 (4.4) 33 (33)	78 (78) 5.2 (5.1) 46 (46)

^aDichotomous and continuous characteristics were compared using the χ^2 test and *t* test, respectively.

^bDichotomous and continuous characteristics were compared using the McNemar test and Wilcoxon signed rank test, respectively.

^cDaily dose of antipsychotic in chlorpromazine equivalents employed just before hospitalization in individuals using antipsychotics.

^dDaily dose of antipsychotic in chlorpromazine equivalents employed at the maximum during hospitalization in individuals using antipsychotics.

*P<.05.

**P<.01.

are listed in Table 2. Before matching, combative behavior was more frequently the reason for hospitalization among the men, while apathy or depression was more frequently the cause for hospitalization among the women. With regard to BPSD, the men were more likely to present as aggressive and have diurnal rhythm disturbances, while the women were more likely to present with paranoid and delusional ideation, hallucination, affective disturbances, and anxieties or phobias. With respect to psychotropic medications (Table 3), the data before matching showed no difference between genders in frequency of use or daily dose of antipsychotics prescribed both before and during hospitalization, while cholinesterase inhibitors were more frequently employed in the women. In the men, the type of antipsychotic treatment most frequently used during hospitalization was quetiapine in 71 (70%), followed by quetiapine plus haloperidol in 10 (10%) and

haloperidol alone in 9 (9%), while among the women, the most frequently used was quetiapine in 95 (67%), followed by haloperidol in 14 (10%) and risperidone in 11 (8%). Other types of antipsychotic medication prescribed included olanzapine, perospirone, and aripiprazole.

Of the 122 male patients, 71 (58%) were favorably discharged. Of the remaining 51 patients, 38 were transferred to a hospital, 8 died during hospitalization, and 5 were in the hospital when the study ended. Of the 170 women, 131 (77%) were favorably discharged, which was a higher frequency than in men (P=.001). Of the remaining 39 patients, 28 were transferred to a hospital, 3 died during hospitalization, and 8 remained hospitalized when the study ended. A Kaplan-Meier survival curve showed that length of hospital stay was longer in the men than in the women (median length = 165 days [95% CI, 118–252 days] vs 89 days [95% CI, 72–118 days], P=.0082) (Figure 1).

After matching on propensity scores, a total of 100 matched pairs were produced. Demographic characteristics of the men are listed in Table 1, which shows that the 2 groups were balanced in terms of age, type of dementia, family style, residency before hospitalization, relationship with caregiver, and MMSE and N-ADL scores.

After matching, combative behavior was more frequently the reason for hospitalization among the men, while overactivity was more frequently the cause of hospitalization among the women. Among BPSD, aggressiveness was more frequently recorded in the men than in the women, while paranoid and delusional

ideation, hallucination, affective disturbance, and anxieties and phobias were more frequent in the women compared to men (Table 2). Use of a cholinesterase inhibitor was more frequent in the women before hospitalization, but the difference disappeared after admission (Table 3). Incidence of favorable discharge was lower in the men than in the women (60% vs 77%, P=.0173), and men were more likely to be hospitalized longer than the women (median length = 165 days [95% CI, 118–262 days] vs 104 days [95% CI, 69–143 days], P=.0127), as shown in the Kaplan-Meier estimation in Figure 2.

DISCUSSION

To our knowledge, this study is the first to demonstrate the effects of gender difference both in the manifestation of BPSD



Figure 1. Cumulative Probability of Hospital Stay Between Men

Figure 2. Cumulative Probability of Hospital Stay Between Men and Women After Matching



and in outcomes among patients hospitalized for treatment of BPSD.

The demographic characteristics of patients in this study before matching revealed different profiles of living situation between genders. In particular, the men had more frequently lived with and been cared for by their partners. On this point, it is also noteworthy that both cognitive and physical functions were more severely impaired in men at the time of admission. A previous study²⁷ found that demented people cared for by spouses were less likely to be institutionalized compared to those cared for by nonspouses. This could reflect the strong commitment to a patient provided by a spouse caregiver, who will generally only give in when social pressure is no longer bearable, whereas nonspouse caregivers might more readily seek professional help. Preexisting advanced physical and cognitive deficiencies might also contribute to the observed lower likelihood of favorable discharge in the men. Thus, seeking intervention by a formal care service from the earlier stages of BPSD may be beneficial in formulating an appropriate care plan to informal (ie, nonprofessional) caregivers of male patients.

It is known that various factors apart from gender could affect the manifestation of BPSD.²⁸⁻³¹ We therefore used a matching strategy to control for individual living situation

and type of dementia, as well as cognitive and physical status, ensuring a proper comparison of BPSD between genders. The strategy also enabled more clear delineation of the relationship between BPSD and the outcomes of inpatient treatment.

Even after matching, paranoid and delusional ideation, affective disturbances, and anxieties and phobias were more frequent in women than in men, which corresponds to the results of some previous studies in community-dwelling elders.⁹⁻¹² While most of the previous studies have failed to demonstrate gender difference in prevalence of hallucination, our data showed clear female preponderance. This divergence in findings may be due to differences in the study populations, in that our group's symptoms might have been more prominent than those reported in community-based studies. On the other hand, aggressiveness and combative behavior were found more frequently in the men, consistent with the results of community-based studies.¹²⁻¹⁸ The higher incidence of aggression in men has been biologically associated with genetic predisposition^{32,33} and hormonal levels.³⁴ The affected frontal inhibition in dementia might also affect the underlying personality patterns.^{12,35}

The women in this study showed a higher rate of favorable discharge and shorter hospital stay than the men. Although we did not evaluate the chronological treatment response in detail, this finding suggested that paranoid and delusional ideation, hallucination, affective disturbances, and anxieties and phobias might respond well to treatment including pharmacotherapy.

However, the efficacy of antipsychotics in controlling aggressive behavior is still controversial,³⁶ despite their widespread use, and these drugs are associated with significant adverse effects. A recent meta-analysis³⁷ concluded that antipsychotics might reduce the frequency of disruptive behavior by only 18%. Unfortunately, safer alternatives^{38,39} with sufficient efficacy remain unavailable.

Aggressiveness remains one of the most distressing behaviors in patients,⁴⁰⁻⁴² and some caregivers might disapprove of a patient's discharge even after symptom remission. More enhanced care strategies or fortified service provision to attenuate such stress may facilitate the caregivers' acceptance in these circumstances. In addition, interventions targeting caregivers have recently emerged, ^{43–45} and the trials indicate that these measures could improve quality of life for patient-caregiver dyads.46,47

The lower likelihood of favorable discharge in men may not be attributable solely to the higher prevalence of aggressiveness. It is also possible that care service is not equally provided between genders and that this has an impact. Indeed, in Japan, 80% of residents in care institutions are women,48 and few beds are usually equipped for use by men. In addition, 78% of care workers in those institutions are women,⁴⁹ and they often prefer acceptance of female residents for the ease of care. Together, these factors could

contribute to the poor availability of institution beds for men. Such gender differences in availability of care resources have yet to be investigated, but studies are clearly warranted.

This study had some limitations that should be acknowledged and addressed. Because the study was retrospective and based on review of medical charts, the available information was limited. While a major concern of the study was the prevalence of each cluster of BPSD at the time of admission, we did not evaluate BPSD newly developed after admission and the occurrence of physical comorbidities potentially associated with BPSD decline (eg, stroke), which could have affected the treatment outcomes. Furthermore, although any pharmacotherapy was optimized to achieve remission of BPSD as soon as possible, our routine practice did not include a detailed evaluation of the treatment response. These issues should be taken into consideration in future studies and practice. This study was conducted in a single institution in a particular region of our country. Welldesigned prospective and larger-scale studies are warranted to confirm our results.

In conclusion, male patients with BPSD were more likely to present with aggressiveness, and this could contribute to the observed lower likelihood of favorable discharge. More effective treatment options for aggressiveness and enhanced care strategies to decrease caregivers' stress could therefore improve the patient outcomes. Future investigations into gender difference in availability of care resources could be crucial. On the basis of these findings, gender differences should be taken into consideration in making decisions about optimal treatment and a care plan for hospitalized patients with BPSD to obtain a better quality of life.

Drug names: aripiprazole (Abilify), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others).

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Gender Differences in Behavioral Symptoms of Dementia

Focus on Alzheimer's Disease and Related Disorders

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Alzheimer's Disease and Related Disorders section. Please contact Eric M. Reiman, MD, at ereiman@psychiatrist.com.