学位論文

Association of premorbid personality with behavioral and psychological symptoms in dementia with Lewy bodies: comparison with Alzheimer's disease patients

（レビー小体型認知症における病前性格と認知症の行動・心理症状の関連：
アルツハイマー型認知症と比較して）

旭川医科大学大学院医学系研究科博士課程

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Association of premorbid personality with behavioral and psychological symptoms in dementia with Lewy bodies: comparison with Alzheimer's disease patients

Premorbid personality and BPSD

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ABSTRACT

Aim: The aim of this study was to elucidate the relationship between premorbid personality traits and behavioral and psychological symptoms in dementia (BPSD) in dementia with Lewy bodies (DLB) and Alzheimer's disease (AD) patients. **Methods:** Forty-one DLB patients and 98 AD patients were assessed for BPSD using the Neuropsychiatric Inventory (NPI). Each patient's midlife personality traits were rated by a family member using the NEO Five-Factor Inventory (NEO-FFI) questionnaire.

Results:

In multiple regression analyses for DLB patients, NPI total score and anxiety were significantly associated with premorbid openness, delusion with premorbid agreeableness, and agitation with premorbid conscientiousness. In AD patients, depression was significantly associated with premorbid neuroticism, and agitation, apathy, and irritability with premorbid agreeableness.

Conclusions: Premorbid personalities affected BPSD differently in DLB and AD.

Given the differences in the effects of premorbid personalities on BPSD, additional studies are needed to develop interventions to reduce these symptoms.

Key words: Alzheimer's disease, behavioral/psychological symptoms in dementia, dementia with Lewy bodies, Neuropsychiatric Inventory, premorbid personality

INTRODUCTION

Dementia with Lewy bodies (DLB) is the second most frequent dementia after Alzheimer's disease (AD) [1], and compared with AD patients, DLB patients develop behavioral and psychological symptoms in dementia (BPSD) at an earlier stage of dementia [2]. DLB patients also develop delusions, hallucinations, apathy, and sleep disturbance beginning in the very mild stage of dementia (Clinical Dementia Rating [3] = 0.5) [2], which can place a burden on caregivers that exceeds that experienced by AD caregivers [2]. Indeed, the caregiver burden from BPSD can be greater than that of the cognitive decline itself, and a recent review article linked BPSD with psychological distress and depression in caregivers [4]. BPSD often lead to the hospitalization or institutionalization of older adults with dementia.

BPSD are the result of biological, psychological, and social factors [5].

Countermeasures to BPSD therefore include medication for biological factors, psychological intervention for psychological factors, and environmental coordination for social factors. A recent review article reported that psychosocial interventions reduced BPSD such as depression and agitation [6].

Among the psychosocial interventions for BPSD is person-centered care, in which the principle idea includes "treating people as individuals" [7]. This approach is helpful for

understanding patient personalities [8]. Several studies have reported relationships between the premorbid personalities of patients and the BPSD they experience. For example, premorbid neuroticism is associated with mood, and premorbid agreeableness is related to agitation, apathy, and irritability in dementia patients, particularly AD patients [9-13]. However, to the best of our knowledge, no studies have explored relationships between premorbid personality and BPSD in DLB patients.

The aim of this study was to investigate and compare the relationship between premorbid personality traits and BPSD in DLB and AD patients.

METHODS

Study Participants

This study included 41 DLB patients and 98 AD patients, all recruited through the memory clinic at our hospital. AD is the most prevalent dementia. Several studies have reported relationships between premorbid personality and BPSD in AD patients. For the comparison to DLB patients, AD patients were recruited for this study.

The patients underwent general physical, neurological, and neuropsychological examinations, including the Mini-Mental State Examination (MMSE) [14]. Structural neuroimaging (head computed tomography or magnetic resonance imaging[MRI]) and

routine laboratory investigations, including those for thyroid function, were also performed. Exclusion criteria included a history of stroke, significant head trauma, alcohol abuse, major psychiatric illness, such as schizophrenia and depression, or evidence of other neurological disorders that compromise cognition.

Clinical diagnoses were made by agreement among three psychiatrists (K.T., F.M., and J.N.) who specialize in dementia. DLB was diagnosed according to the consensus criteria for DLB, [15] and the diagnosis of AD was made according to the National Institute on Aging-Alzheimer's Association workgroups criteria[16].

BPSD and Premorbid Personality Assessment

BPSD were assessed during the first medical examination at the hospital through a face-to-face interview with a family member or other caregiver in regular current contact with the patient. The patients' premorbid personalities were assessed through face-to-face interviews with the same family members. These family members included 38 spouses and 101 children.

Ethics

This study was approved by the Institutional Ethical Board for Epidemiological Studies

of Asahikawa Medical University. All patients gave informed consent, and their anonymity was preserved.

Measures

BPSD were evaluated using the Neuropsychiatric Inventory (NPI) [17, 18], which contains 10 subscales of BPSD: delusion, hallucination, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behavior. For each of these subscales, the family member or caregiver was asked to rate the severity from 0 to 3 and the frequency from 0 to 4. NPI composite scores were calculated by multiplying the severity and frequency scores; the possible composite scores therefore ranged from 0 to 12 for each subscale. The total NPI score was obtained by summing the scores across the 10 domains.

For the assessment of each patient's premorbid personality, the family member completed the NEO Five Factor Inventory (NEO-FFI) [19] in a face-to-face interview with hospital clinical psychologists. This inventory is based on the Five-Factor Model of personality, which is widely used in personality research and comprises the domains of neuroticism, extraversion, openness, agreeableness, and conscientiousness. The NEO-FFI has been shown to be a reliable retrospective measure of premorbid personality in AD patients [20].

The family members were given the following instruction: for each statement, please choose the response that best represents your opinion of how you remember your relative in his or her 40s. The NEO-FFI contains 12 items relating to each of the five personality domains, and each item is rated on a five-point scale (strongly disagree, disagree, neutral, agree, and strongly agree). Scores range from 0 to 4 for each item and the maximum total score for each domain is 48.

Statistical Analyses

Associations of the premorbid personality factors of neuroticism, extraversion, openness, agreeableness, and conscientiousness with the individual NPI domains and the total NPI score were evaluated using Pearson's correlational analysis. Multiple regression analyses were carried out with the individual NPI domains and total NPI score as dependent variables, using the backward elimination method, with the premorbid personality factors of neuroticism, extraversion, openness, agreeableness, and conscientiousness as independent variables. Age, sex, and MMSE score were added to the models as forced-entry variables. The analyses were performed using IBM SPSS Statistics 21.0 for Windows (IBM Corp., Armonk, NY).

RESULTS

The demographic and clinical characteristics of the participants are shown in Table 1. The DLB patients were older than the AD patients and had completed fewer years of education. The DLB patients had lower MMSE scores and higher NPI total scores.

Crude Analysis

Tables 2 and 3 show the correlations of premorbid neuroticism, extraversion, openness, agreeableness, and conscientiousness with the individual NPI domains and NPI total score. In the DLB patients, premorbid openness was significantly negatively related to total NPI score and anxiety, premorbid conscientiousness was significantly positively related to agitation. In the AD patients, premorbid neuroticism was significantly positively related to depression, premorbid extraversion was significantly negatively related to apathy, premorbid openness was significantly negatively related to irritability, and premorbid agreeableness was significantly negatively related to apathy and irritability.

Multiple Regression Analysis

Table 4 presents the multiple regressions analysis for the DLB patients. The score for premorbid openness was significantly negatively associated with the total NPI score

(partial regression coefficient [B]) = −1.504, 95% confidence interval [CI]: −2.771 to −0.237) and with the NPI score for anxiety (B = −0.263, 95% CI: −0.505 to −0.022). The score for premorbid agreeableness was significantly negatively associated with the NPI score for delusion (B = −0.325, 95% CI: −0.611 to −0.038). The score for premorbid conscientiousness was significantly positively associated with the NPI score for agitation (B = 0.220, 95% CI: 0.046 to 0.394).

Table 5 presents the multiple regression analysis for the AD patients. The score for premorbid neuroticism was significantly positively associated with the NPI score for depression (B = 0.090, 95% CI: 0.011 to 0.168). The score for premorbid agreeableness was significantly negatively associated with the NPI scores for agitation (B = −0.095, 95% CI: −0.184 to −0.007), apathy (B = −0.133, 95% CI: −0.244 to −0.022), and irritability (B = −0.090, 95% CI: −0.169 to −0.011).

DISCUSSION

We investigated the relationships between premorbid personality and BPSD in DLB and AD patients. The adjusted multiple regression analysis for DLB patients showed significant associations of premorbid openness with NPI total score and anxiety, premorbid agreeableness with delusion, and premorbid conscientiousness with agitation.

In AD patients, the adjusted multiple regression analysis showed significant associations of premorbid neuroticism with depression, premorbid agreeableness with agitation, apathy, and irritability. These results suggested that low premorbid agreeableness in DLB patients may lead to later psychological symptoms such as delusion, whereas in AD patients, it may lead to later behavioral symptoms such as agitation, apathy, and irritability.

Multiple factors contribute to the appearance of BPSD. Animal studies can investigate the cognitive symptoms of dementia such as memory loss, but studying the relationship between personal traits and psychiatric symptoms is difficult in animals. Therefore, the mechanisms of these relationships have not been fully elucidated. A review article [21] about the neurobiological basis of BPSD among AD patients mentioned that psychopathological, neuropsychological, biochemical and psychophysiological methods have been used to study behavioral and psychiatric problems.

Relationships between BPSD and functional and pathological brain changes have been

reported. Studies of DLB patients using brain perfusion single-photon emission tomography and ^{18}F-fluoro-2-deoxy-glucose positron-emission-tomography showed that delusion was associated with dysfunction of the frontal cortex [22] and hypometabolism of the right frontal cortex[23]. In AD patients, apathy was associated with a pathological change in the anterior cingulate bilateral frontal cortex according to the results of structural MRI [24], agitation was associated with hypometabolism of the frontal and temporal lobes based on the results of the positron emission tomography[25], and pathological changes in the insula and the anterior cingulate cortex were observed with structural MRI. [24] Thus, frontal lobe changes were related to delusion in DLB and to apathy and agitation in AD. Although the detailed mechanism is unknown, these differences may be related to differences in the associations of premorbid personality with BPSD between DLB and AD.

Compared with AD patients, DLB patients reportedly have higher NPI total scores and a greater frequency of delusion, hallucination, and anxiety. [2] High scores with wide distributions had more statistical power in regression analysis. These results support our finding of that premorbid personality had significant effects on NPI total score, delusion, and anxiety in DLB patients.

One large-sample study in AD patients [9] reported that neuroticism showed no

significant relationship to “affect,” an outcome that combine elation, anxiety, and depression. However, consistent with our findings, several studies [10-13] showed a positive relationship between premorbid neuroticism and depression. Thus, because the former study used a combined outcome, not depression alone, we believe that premorbid neuroticism can affect depression in AD patients. We also found significant negative relationships between premorbid agreeableness and agitation, apathy, and irritability in AD patients, and these results were also similar to those of a previous study. [9] Therefore, we hypothesized that there are differences between DLB and AD patients in the associations of premorbid personality with BPSD, although their mechanisms remain unknown.

Multiple factors contribute to the appearance of BPSD, including biological factors (such as neurochemical abnormalities and neuropathological changes of the brain), social factors (such as family history, domestic arrangements, and institutionalization), and psychological factors (such as past psychiatric history, and premorbid personality) [5]. Thus, BPSD may be influenced by these psychological factors as premorbid personalities, although the magnitude of the effects of psychological and biological factors on BPSD may vary among the different types of dementia. Our study did not evaluate biological factors, and additional studies of BPSD that evaluate biological and psychological factors

simultaneously are needed.

We investigated the relationship between premorbid personality and BPSD in DLB and AD patients and found that these relationships likely differ between types of dementia. The study participants included patients with the major dementia subtypes DLB and AD, but in other types of dementia, such as vascular dementia and frontotemporal dementia, premorbid personality may have a different effect on BPSD, although a previous study reported no significant relationship between premorbid personality and BPSD in frontal lobe dementia patients [26].

According to a recent review of personalized psychosocial interventions for behavioral and psychological symptoms [6], evidence supports the value of personalized pleasant activities in the treatment of agitation, and reminiscence therapy to improve mood. A cluster randomized controlled trial reported that person-centered care reduced agitation in patients at Australian residential care sites [27, 28]. The principle idea of person-centered care consists of four factors[7], one of which treating people as individuals. Tom Kitwood, who proposed person-centered care, emphasized the importance of recognizing the uniqueness of each person through the exploration of personality[8]. However, previous person-centered care interventions did not include the recognition of premorbid personality in detail. Because premorbid personality may predict the types of BPSD that

develop, adding premorbid personality evaluations to person-centered care may help reduce BPSD.

This study has several limitations. First, the BPSD symptoms and premorbid personality of each patient were assessed on the basis of information from a single individual. However, these individuals were family members or other caregivers who had regular current contact with the patient, and the assessment was conducted through a face-to-face interview at the hospital. Individual responses to the NEO-FFI reportedly have adequate reliability, even when the inventory is used as a questionnaire [9, 20]. The same informants provided both the NPI score and the NEO-FFI score for their respective relatives, and the evaluation of personality traits may be affected by the current status of the patient. However, other recent studies, have used the same informants to provide both scores [9, 10, 13]. Thus, in retrospective hospital-based studies, current informants are needed to evaluate personality traits. Therefore, we used interviewers (not paper-based questionnaires) to obtain both scores that considered the patients' prior personality traits. Second, the study was restricted to one hospital in Japan; however, this facility is the dementia center for the region. Third, the sample size was relatively small. However, the prevalence of DLB is lower than that of AD. The sample size of previous studies of AD patients included between 28 and 410 participants [9-13, 29, 30]. Although we used the backward

elimination method and needed to introduce premorbid personality variables separately in the models, we believe the significant results have clinical meaning because they were adjusted by age, sex, and MMSE score. Fourth, our study could not clarify the mechanism through which BPSD develops. A recent review of BPSD [5] reported that apathy was related to structural changes of the anterior cingulate gyrus, but depression was not related to a specific structural brain region. The author stated that neuropathology alone cannot account for the heterogeneity of BPSD, which is influenced by various factors, including premorbid personality. Finally, as previously mentioned, biological factors were not included in the models.

In conclusion, premorbid personality traits affected BPSD symptoms differently in DLB and AD patients. Further research considering neurochemical abnormalities and genetic susceptibility is needed to elucidate the association between premorbid personality and BPSD.

DISCLOSURE STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conception and design of the study: K.T., Y.S., E.Y.

Acquisition and analysis of data: K.T., F.M., J.N.,

Drafting the manuscript: K.T., Y.S., E.Y., Y.K., Y.N., T.Y.

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Table 1. Patient demographics and clinical characteristics

	DLB (n = 41)	AD (n = 98)	*P* value
Age, years	83.3 ± 6.20	80.6 ± 5.66	0.015 [a]
Male, n (%)	11 (26.8)	32 (32.7)	0.320[b]
Years of education, years	7.9 ± 2.22	9.4 ± 2.43	0.001 [a]
Living situation, community-dwelling, n (%)	33 (80.5)	91 (92.9)	0.036[b]
MMSE score	16.8 ± 5.90	19.9 ± 4.94	0.002 [a]
NPI total	25.6 ± 21.46	13.9 ± 16.17	0.001 [a]

Variables are presented as means ± SD (standard deviation or number [%]).

AD: Alzheimer's disease; DLB: dementia with Lewy bodies; MMSE: Mini-Mental State Examination; NPI: Neuropsychiatric Inventory.

[a] *t*-test.

[b]Chi-square test.

Table 2. Pearson's correlations between premorbid personality traits and behavioral and psychological symptoms in patients with Alzheimer's disease.

(N = 98)	NPI total	Delusions	Hallucination	Agitation	Depression	Anxiety	Elation	Apathy	Disinhibition	Irritability	Aberrant motor behavior
Neuroticism	0.152	0.107	0.061	0.141	0.241*	0.123	−0.044	0.103	0.165	0.086	−0.012
Extraversion	−0.110	−0.107	−0.091	−0.079	−0.111	−0.026	−0.056	−0.199*	−0.001	−0.088	0.110
Openness	−0.127	−0.086	−0.074	−0.127	−0.163	−0.114	−0.118	−0.122	−0.006	−0.213*	0.021
Agreeableness	−0.180	−0.129	0.046	−0.182	−0.108	0.112	−0.073	−0.239*	−0.116	−0.210*	−0.101
Conscientiousness	0.045	0.107	−0.046	0.149	−0.096	0.122	−0.074	−0.060	0.024	0.136	0.112

* $P < 0.05$, ** $P < 0.01$.

NPI: Neuropsychiatric Inventory.

Table 3. Pearson's correlations between premorbid personality traits and behavioral and psychological symptoms in patients with dementia with Lewy bodies.

(N = 41)	NPI total	Delusions	Hallucination	Agitation	Depression	Anxiety	Elation	Apathy	Disinhibition	Irritability	Aberrant motor behavior
Neuroticism	−0.187	−0.223	−0.254	−0.290	0.085	0.181	−0.060	−0.011	−0.201	0.015	−0.267
Extraversion	−0.148	−0.089	−0.044	−0.066	−0.034	−0.085	−0.174	−0.045	−0.045	−0.169	−0.115
Openness	−0.363*	−0.226	−0.264	−0.274	−0.058	−0.343*	−0.221	−0.243	−0.126	−0.115	−0.241
Agreeableness	−0.242	−0.285	−0.046	−0.275	0.101	−0.254	−0.054	−0.243	−0.045	−0.065	−0.133
Conscientiousness	0.260	0.136	0.240	0.434**	0.087	0.105	−0.100	0.251	0.209	−0.003	0.068

* $P < 0.05$, ** $P < 0.01$.

NPI: Neuropsychiatric Inventory.

Table 4. Multiple regression analyses with NPI scores as dependent variables and premorbid personality traits as independent variables in patients with dementia with Lewy bodies.

		B	β	95% CI	p value
NPI total	Openness	−1.504	−0.347	−2.771 to −0.237	0.021
Delusion	Neuroticism	−0.196	−0.283	−0.409 to 0.017	0.071
	Agreeableness	−0.325	−0.367	−0.611 to −0.038	0.028
Hallucination	Openness	−0.237	−0.265	−0.509 to 0.035	0.085
Agitation	Conscientiousness	0.220	0.383	0.046 to 0.394	0.015
Depression	—[a]				
Anxiety	Openness	−0.263	−0.346	−0.505 to −0.022	0.033
Elation	—[a]				
Apathy	Agreeableness	−0.195	−0.273	−0.428 to 0.038	0.098
Disinhibition	—[a]				
Irritability	—[a]				
Aberrant motor behavior	—[a]				

Note: Age, sex, and Mini-Mental State Examination score were added to the models as forced entry variables for adjustment.

B: partial regression coefficient; β: standardized partial regression coefficient; 95% CI: 95% confidence interval for the partial regression coefficient; NPI: Neuropsychiatric Inventory.

[a] No premorbid personality factor selected.

Table 5. Multiple regression analyses with NPI scores as dependent variables and premorbid personality traits as independent variables in patients with Alzheimer's disease.

		B	β	95% CI	p value
NPI total	Agreeableness	−0.420	−0.188	−0.871 to 0.032	0.068
Delusion	—[a]				
Hallucination	—[a]				
Agitation	Agreeableness	−0.095	−0.222	−0.184 to −0.007	0.034
	Conscientiousness	0.088	0.183	−0.010 to 0.187	0.078
Depression	Neuroticism	0.090	0.232	0.011 to 0.168	0.026
Anxiety	Neuroticism	0.085	0.206	−0.012 to 0.182	0.086
	Agreeableness	0.083	0.211	−0.010 to 0.176	0.080
Elation	—[a]				
Apathy	Agreeableness	−0.133	−0.245	−0.244 to −0.022	0.019
Disinhibition	—[a]				
Irritability	Openness	−0.083	−0.172	−0.180 to 0.015	0.095
	Agreeableness	−0.090	−0.238	−0.169 to −0.011	0.025
	Conscientiousness	0.081	0.190	−0.006 to 0.168	0.069
Aberrant motor behavior	—[a]				

Note: Age, sex and Mini-Mental State Examination score were added to the models as forced entry variables for adjustment.

B: partial regression coefficient; β: standardized partial regression coefficient; 95% CI: 95% confidence interval for the partial regression coefficient;

NPI: Neuropsychiatric Inventory.

[a] No premorbid personality factor selected.