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Relationship with Bipolar Temperament and Behavioral and Psychological Symptoms of Dementia in Alzheimer's Disease

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Abstract

Objects: To evaluate the relationship between bipolar temperament (BT) and the behavioral and psychological symptoms of dementia (BPSD) in Alzheimer's disease (AD).

Backgrounds: In Japan, no medicine is permitted for BPSD in AD. And there was no study that evaluated the relationship BT and BPSD in AD.

Methods and Results: We evaluated 65 AD patients using demographic data (sex, educational level, age at dementia onset, age at the time of test and duration of illness), BP, cognitive function, existence of BPSD and morphologic features in the brain using MRI ($p<0.05$). BPSD was be related with BT. Lower educational level was related with BPSD among those with BT ($p<0.05$).

Conclusions: BPSD in AD was related with BT and among those with BT lower educational level was related with BPSD. We considered that brain reserve (BR) and cognitive reserve (CR) were related with BPSD in AD. We concluded that some kinds of BPSD were related with BR and CR and that there is a possibility that heightening CR might prevent BPSD.

Keywords: Alzheimer's Disease (AD); Behavioral and Psychological Symptoms of Dementia (Bpsd); Bipolarity; Brain reserve; Cognitive reserve

Introduction

Behavioral and psychological symptoms of dementia (BPSD) are important symptoms because these cause caregivers burdens and adverse effects both in patients and caregivers [1]. However, no medications for the treatment of BPSD in patients with Alzheimer's disease (AD) are licensed. In clinical setting, although atypical antipsychotics are avoided because of the increased mortality rate in patients with AD [2], antipsychotics for BPSD symptoms such as delusions, hallucinations, agitation, or aggression are prescribed with consent from the legal representatives of AD patients.

We previously reviewed our articles those reported the effects of aging and disease progress on BPSD and showed that effects of aging and disease progress caused the connections of the mood cluster (anxieties and affective disturbances) with the psychiatric cluster (delusions and hallucinations) and aggressiveness and that BPSD in AD was similar with bipolar features of mixed type or psychotic depression. We might prescribe medications for augmentation of depression to BPSD in AD [3]. Moreover, these features were related with bipolar features, i.e., bipolar temperament (BT), bipolarity or bipolar spectrum. In fact, Ng et al. [4] and Dorey et al. [5] commented that BPSD was related with bipolar disorder. If so, some kinds of BPSD were treatable because BPSD caused by bipolarity that was not be related with direct AD pathology might be possible to be ameliorated by treatment. Therefore, main aim of this study is to investigate treatment direction by clarifying the relationship between BPSD and BT and in patients with BT, which factors was related with BPSD.

Subjects and Methods

Sixty five patients with AD who regularly visited department of Neuropsychiatry Showa University Fujigaoka Hospital (Yokohama, Japan) on May 1, 2013 were enrolled in this study. All subjects met the diagnostic criteria for probable AD assessed with a scale developed by a working group of the National Institute of Neurological and Communicative Disorders and Stroke in collaboration with the Alzheimer's Disease and Related Disorders Association [6]. Exclusion criteria were patients diagnosed with other psychiatric disorders such as schizophrenia and depression before the onset of dementia, those with cerebral hemorrhage or infarction, with active physical symptoms or with severe physical illnesses and those were contraindicated with magnet resonance image (MRI) such as with pacemakers.

We evaluated demographic data (sex, educational level, age at dementia onset, age at the time of test and duration of illness), bipolar temperament (BT), cognitive function, existence of BPSD and morphologic features in the brain using MRI. BT was evaluated using the criteria by the Akiskal and Mallya Affective Temperaments questionnaires [7]. However, because Gassab et al. [8] reported that hyperthyrmic and cyclothymic temperaments were related with bipolar disorder, we only evaluated hyperthyrmic and cyclothymic temperaments. We evaluated BT as "yes (at least one hyperthyrmic and cyclothymic temperament was existed. BT (+))" or "no" (no

hyperthyrmic and cyclothymic temperament, BT (−)), i.e., we divided all patients with bipolar temperament (BT (+)) and without bipolar temperament (BT (−)). Cognitive function was evaluated with the Mini-Mental State Examination (MMSE) [9], which measures global cognitive function in eleven cognitive domains such as orientation (time), orientation (place), registration, attention/calculation, recall, naming, repeat, listen and obey, write and obey, write sentence, paxis. Maximum scores of MMSE is 30 and higher scores is related with better cognitive functions. BPSD were assessed by the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) [10], which measures behavioral and psychological symptoms in seven symptom domains such as paranoid and delusional ideation, hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbance, and anxieties and phobias. BEHAVE-AD is scored on a four-point scale according to the severity of disease. We evaluated BPSD as "yes (at least one BPSD in this scale. BPSD (+))" or "no" (no BPSD in this scale, BPSD (−)). The volumes of Hippocampus by way of MRI were quantitative using voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) [11]. All clinical data were collected using chart review and sometimes using interview with their family members (almost all were their children or their spouses).

We compared all clinical data between in the BPSD (+) and BPSD (−), BPSD (+) and BPSD (−) in BT (+) and BT (−). The statistical analysis comparing group means was conducted using $\chi 2$ with categorical values and Student's t-test with continuous values.

The data were analyzed by a statistical software package SPSS-12.0J (Statview Inc, Tokyo, Japan). We obtained informed consent from all study subjects or their proxies before conducting the study. This study was approved by the Ethical Committee of the Showa University Fujigaoka Hospital.

Results

Table 1 shows the demographic data (sex, educational level, age at dementia onset, age at the time of test and duration of illness), BT, MMSE scores and VSRAD of the BPSD (+) and the BPSD (-) groups.

	BPSD (+)	BPSD (-)	p value
Number (Male/ female)	30 (14/16)	35 (13/22)	0.5974
Educational levels: years	12.7 (2.6)	13.1 (2.3)	0.1610
Age at dementia onset: years	75.6 (5.5)	76.5 (6.1)	0.5055
Age at time of test: years	78.1 (5.4)	78.7 (6.1)	0.6844
Duration: years	2.5 (2.1)	2.1 (1.4)	0.3768
BT+/-	21/9*	14/21	0.0298
MMSE score	19.7 (5.2)*	20.2 (5.6)	0.6951
VSRAD	2.83 (1.25)	2.99 (1.23)	0.6238

Table 1: Demographic data (sex, educational level, age at dementia onset, age at time of test and duration of illness), bipolarity, cognitive function, existence of BT and VSRAD in BPSD (+) group and BPSD (-) group. Data are given as mean (SD) except for number of patients. BPSD (+): behavioral and psychological symptom of dementia positive BPSD (-): behavioral and psychological symptom of dementia negative BT: bipolar temperament, MMSE: Mini-Mental State Examination, VSRAD: voxel-based specific regional analysis system for Alzheimer's disease, *: p<0.05

There were no significant differences in sex distribution, educational level, age at onset of dementia, age at the time of test, duration of illness, VARAD and MMSE scores between in the BPSD (+) group and in the BPSD (-) group. However, BT was more frequent in the BPSD (+) group than in the BPSD (-) group (P<0.05).

Table 2 shows the demographic data (sex, educational level, age at dementia onset, age at the time of test and duration of illness), MMSE scores and VSRAD of the BPSD (+) and the BPSD (-) groups in BT (+) group.

There were no significant differences in sex distribution, age at onset of dementia, age at the time of test, duration of illness, VARAD and MMSE scores between in the BPSD (+) group and in the BPSD (-) group. However, educational level was higher in the BPSD (-) group than in BPSD (+) group (P<0.05).

	BPSD (+)	BPSD (-)	p value
Number (Male/ female)	21 (9/12)	14 (4/10)	0.6100
Educational levels: years	12.1 (2.5)	14.0 (1.6)*	0.0166
Age at dementia onset: years	75.9 (5.7)	79.9 (5.7)	0.3215
Age at time of test: years	78.1 (5.9)	79.9 (6.1)	0.3974
Duration: years	2.2 (1.7)	1.9 (1.1)	0.5493
MMSE score	20.0 (5.1)	21.5 (4.6)	0.3643
VSRAD	2.88 (1.39)	2.75 (1.27)	0.8306

Table 2: Demographic data (sex, educational level, age at dementia onset, age at time of test and duration of illness), bipolarity, cognitive function, existence of BP and VSRAD in BPSD (+) group and BPSD (-) group with BT. Data are given as mean (SD) except for number of patients. BPSD (+): behavioral and psychological symptom of dementia positiveBPSD (-): behavioral and psychological symptom of dementia negative BT: bipolar temperamentMMSE: Mini-Mental State ExaminationVSRAD: voxel-based specific regional analysis system for Alzheimer's disease, *: p<0.05

	BPSD (+)	BPSD (-)	p value
Number (Male/ female)	9 (5/4)	21 (9/12)	0.8107
Educational levels: years	12.7 (2.8)	12.5 (2.5)	0.8901
Age at dementia onset: years	74.8 (5.2)	75.6 (6.2)	0.7250
Age at time of test: years	77.9 (4.5)	77.9 (6.4)	0.9894

Duration: years	3.1 (2.9)	2.2 (1.5)	0.2840
MMSE score	19.1 (5.8)	19.4 (6.1)	0.9109
VSRAD	2.74 (0.91)	3.13 (2.74)	0.4122

Table 3: Demographic data (sex, educational level, age at dementia onset, age at time of test and duration of illness), bipolarity, cognitive function, existence of BP and VSRAD in BPSD (+) group and BPSD (-) group without BT. Data are given as mean (SD) except for number of patients. BPSD (+): behavioral and psychological symptom of dementia positiveBPSD (-): behavioral and psychological symptom of dementia negative BT: bipolar temperament MMSE: Mini-Mental State Examination VSRAD: voxel-based specific regional analysis system for Alzheimer's disease, *: $p<0.05$

Table 3 shows the demographic data (sex, educational level, age at dementia onset, age at the time of test and duration of illness), MMSE scores and VSRAD of the BPSD (+) and the BPSD (-) groups in BT (-) group.

There were no significant differences in sex distribution, educational level, age at onset of dementia, age at the time of test, duration of illness, VARAD and MMSE scores between in the BPSD (+) group and in the BPSD (-) group.

Discussion

In this article we showed that although there were no significant differences in sex distribution, educational level, age at onset of dementia, age at the time of test, duration of illness, VARAD and MMSE scores, BT was significantly more frequent in the BPSD (+) group than in the BPSD (-) group. Moreover, there were no significant differences in sex distribution, age at onset of dementia, age at the time of test, duration of illness, VARAD and MMSE scores, however, educational level was higher in the BPSD (-) group than in BPSD (+) group ($P<0.05$) in BT (+) group. We speculate that BPSD might be related with BP and that appearance of BPSD might be prevented by cognitive reserve (CR) [12].

As for BT, our report is consist with those commented that there were several commonalities in pathophysiological processes of bipolar disorders by Ng et al. [4] and that some BPSD could be the consequence of both dementia and an undiagnosed comorbid bipolar disorder, or pre-existing bipolar diathesis pathoplastically altering the clinical expression of dementia by Dorey et al. [5]. Moreover, our previous reports those showed the mood cluster becomes connected to the psychiatric cluster and aggressiveness according to that the patients with AD become older and AD progresses. We are now convinced the suggestion on treatment of AD from our clinical implications in our previous report [13,14]. And we might prescribe "augmentation" medications for BPSD because BPSD is related with BT [3].

As for educational level, we considered that CR was also related with BPSD. CR is defined as an ability to compensate for dysfunctions caused by pathological processes in central nervous system [10]. In AD, CR might explain the discrepancy between pathological severity of AD and its clinical phenotype and CR prevented form the onset of AD and cognitive decline was downregulated by CR [15]. Kartzman reported that education was one of the most important factors those attributed to CR [16]. In this also we also reported that in BT (+) patients with AD educational level which is thought to be related with CR [15] was related with BPSD. Therefore we speculated that CR was related not only with the onset of AD and the downregulation of cognitive decline but also with BPSD. In fact, Xu et al. commented that CR was considered to be related with noradrenergic function and BPSD in AD [17] was reported to be caused by noradrenergic dysfunction by loss of noradrenergic neuronal cells [18]. Moreover, reported that delirium was related with CP and was prevented by heightening CR [19].

Moreover, brain reserve (BR) might also be related BT. BR is brain size or neuronal count that explains the individual differences between degree of inserts and real pathological structures [10]. Because certain characters were reported to be related with brain structure [20], we speculated that BT might be related with brain structure (BR). From these points of view, we speculated that on the base of poor BR, low CR caused BPSD in AD patients because BPSD in AD was related with BT and among those with BT lower educational level was related with BPSD. Therefore, some kinds of BPSD were related with BC and that there is a possibility that heightening CR might prevent BPSD. We could not elucidated which BPSD was related with BT because of small sample size. However, according to our previous reports, delusion, hallucination, and aggressiveness might be related with BT because these symptoms were connected with affective disturbance and anxiety caused by aging and disease (AD) progression [3,13]. These symptoms (delusion, hallucination and aggressiveness) might be treatable by heightening CR.

The limitations of this study included: a small sample size, that this study was a cross-sectional one, with no longitudinal course and that we selected the outpatients who visited psychiatric outpatient clinic (selection bias). Therefore, further investigations would be necessary to delineate a more precise relationship between BP and clinical symptoms, especially BPSD. Moreover, we need to evaluate the effects of CR on BPSD in AD patients with BT using longitudinal observations of large samples in order to elucidate which BPSD was related with BT. These studies through light to the treatments of BPSD.

Conclusion

BPSD in AD was related with BT and among those with BT lower educational level was related with BPSD. We considered that BR and cognitive reserve (CR) were related with BPSD in AD. Farther study is needed to confirm our results with larger samples.

Conflict of Interest

Koji Hori received lecture fees from Eisai Co., Ltd.; Pfizer Japan Inc.; Novartis Pharma K.K.; Daiichi Sankyo Inc.; Ono Pharmaceutical Co., Ltd.; Janssen Pharmaceutical K.K.; Yoshitomi Yakuhin Co.; and Mitsubishi Tanabe Pharma Co. Mitsugu Hachisu received funding from Astellas Pharma Inc.; Meiji Seika Pharma Co., Ltd.; Dainippon Sumitomo Pharm Co., Ltd.; Eli Lilly Japan K.K.; and Shionogi & Co., Ltd.. He also received lecture fees from Meiji Seika Pharma Co., Ltd. and Mitsubishi Tanabe Pharma Co.

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