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Gender Difference in Behavioral and Psychological Symptoms of Alzheimer's Disease

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Abstract

Behavioral and psychological symptoms of dementia (BPSD) are important clinical manifestations of Alzheimer's Disease (AD), which may occur at the early stage or throughout the entire course of dementia. They can predict the progression of dementia and serve as the major causes for long-term hospitalization and reduction in caregiver's life quality. Current studies on gender difference of AD are only limited to the epidemiological aspect, but rarely on the clinical and neuropathology aspect. The present study discussed gender differences in BPSD of AD patients and whether white matter hyperintensity was significant associated with BPSD. We divided a total of 76 patients diagnosed with Alzheimer's disease according to DSM-IV-TR into groups with male and female dementia. Then we examined whether there were differences in BPSD, cognitive function and cerebral white matter hyperintensity (WMH) between groups. Our results showed a significant gender differences in delusion, anxiety, sleep behavior disorder, verbal ability and attention ($p < 0.05$). The results of Regression Analysis showed that only WMH score entered the equation at last ($t = 2.451$, $p = 0.020$), while the other variables were removed from the equation, such as Gender ($t = -0.315$, $p = 0.755$), Course of disease ($t = -0.679$, $p = 0.503$), CDR ($t = 0.809$, $p = 0.425$). The result of this study indicated that certain gender differences exist in behavioral and psychological symptoms of Alzheimer's disease. At the same time, cerebral white matter lesions were independently associated with BPSD in Alzheimer's disease patients.

Keywords

Alzheimer's disease, Behavioral and psychological symptoms of dementia (BPSD), Gender differences, White matter hyperintensity (WMH)

Introduction

Alzheimer's Disease is a neurodegenerative disease featured by occult onset and progressive cognitive impairment. It is the leading cause of dementia, comprising up to 60%-80% of cases [1,2]. Behavioral and psychological symptoms of dementia are important clinical manifestations of Alzheimer's Disease, which may occur at the early stage or throughout the entire course of dementia. They can predict the progression of dementia and serve as the major causes for long-term hospitalization and reduction in caregiver's life quality [3,4]. Current studies on the gender difference of AD are only limited to the epidemiological aspect, but rarely on the clinical and neuropathological aspect [5]. The present study discussed gender differences in BPSD of AD patients and whether white matter hyperintensity was significant associated with BPSD.

Methods

Study subjects

The present study was performed in Affiliated Brain Hospital of Guangzhou Medical University from December 2012 to February 2015 (N = 76 patients). The study protocol, informed consents were approved by the Institutional Review Board of Affiliated Brain Hospital of Guangzhou Medical University.

76 Alzheimer's disease patients with BPSD as the main complaints were recruited in the study. The inclusion criteria were as follows: (1) The patients was diagnosed with Alzheimer's disease based on the criteria of the fourth

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revised edition of the Diagnostic and Statistic Manual of Mental (DSM-IV-TR); (2) Also based on the criteria for AD proposed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA); (3) Present BPSD already affecting the social functions of the patients; (4) The patients or relatives having signed the informed consent. Patients meeting any of the following criteria were excluded from the study: patients accompanying other mental disorders, such as schizophrenia, schizoaffective disorders, delusional disorder, affective disorder and alcohol or substance dependence.

Methods

Assessment scale: The psychiatrist investigated the patients' medical history and collected baseline data and results of physical examination, neurological examination, psychiatric examination and clinical diagnosis before the inclusion. The "different genders" in our study only refer to the biological based dichotomized distinction of males vs. females.

Neuropsychiatric Inventory (NPI): This tool was developed to assess the BPSD of dementia patients. It measures the severity and frequency of patients' abnormal behaviors in a total of twelve fields as well as the stress of caregivers, which includes Delusion, Hallucination, Agitation/Aggression, Depression, Anxiety, Euphoria/Elation, Apathy/Indifference, Disinhibition, Irritability/Lability, Aberrant Motor Behavior, Sleep/Nighttime Behavior and Appetite/Eating Changes. Higher scores indicate more severe problem behaviors.

Clinical Dementia Rating Scale (CDR): This scale was used to determine the severity of cognitive impairment. The CDR scores range from 0.5 to 3. (CDR = 0 Healthy, 0.5 point for Questionable dementia, 1 point for Mild dementia, 2 points for Moderate dementia, 3 points for Severe dementia).

Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog): ADAS-cog is the most widely used measure of cognitive performance in AD clinical trials. It includes 12 components (Word recall, Naming objects and fingers, Commands, Constructional praxis, Ideational praxis, Orientation, Word recognition, Remembering test instruction, Ability of spoken language, Word finding, Comprehension, Attention). A total ADAS-cog score ranges from 0 (best cognitive performance) to 70 (worst performance).

Detection of White Matter Hyperintensity (WMH) on MRI: A total of 37 patients diagnosed with AD were recruited to the further study. Patients were divided into two groups, namely, none to mild WMH group (0-2 points, n = 14) and moderate to severe WMH group (3-6 points, n = 23) by magnetic resonance imaging (MRI) scans. WMH was quantified using the Fazekas scale according to T2 and FLAIR (fluid-attenuated inversion recovery) - weighted images.

Fazekas scores were used to evaluate WMH on the T2 and FLAIR-weighted images on a 0-6 score scale. Hyperintensity around the ventricles and deep WMH were assessed on the FLAIR images. The total score was the sum of the two subscores. Scoring criteria for periventricular (PV) -WMH were as follows: 0 point, no lesions; 1 point, cap-like or pencil-like thin slice lesions; 2 points, lesion presenting as a smooth halo; 3 points, irregular periventricular hyperintensity, extending into the deep white matter. Deep subcortical (DW) WMH: 0 point, no lesions; 1 point, spot-like lesions; 2 points, initial signs of lesions merging; 3 points, extensive lesions merging [6]. WMH grading: 0 point, no WMH; 1-2 points, mild; 3-4 points, moderate; 5-6 points, severe.

The image data were processed by medical imaging specialist, who was blinded to the clinical data of the subjects, so as to avoid bias.

Statistics: Measurement data were expressed as Mean ± S.D deviation. Intergroup comparisons of measurement data were conducted by performing an independent t-test, and categorical variables were assessed by Chi-square test. Then Multiple Linear Stepwise Regression Analysis was used to eval-

Table 1: Gender differences in demographic and NPI scores of AD patients.

	Male Group (n = 27)	Female Group (n = 49)	*t*	*p*
Age (year)	74.44 ± 9.88	75.06 ± 9.70	-0.264	0.793
Education (year)	8.26 ± 4.95	6.47 ± 4.69	1.549	0.126
Course (month)	51.27 ± 31.77	40.93 ± 25.36	1.433	0.157
Delusion	1.85 ± 4.11	4.35 ± 4.77	-2.389	0.020*
Hallucination	2.19 ± 3.53	2.92 ± 4.21	-0.767	0.445
Agitation/Aggression	5.89 ± 4.62	3.94 ± 4.22	1.866	0.066
Depression/Dysphoria	1.52 ± 3.06	2.02 ± 3.26	-0.657	0.513
Anxiety	0.93 ± 1.94	2.43 ± 4.01	-2.197	0.031*
Euphoria/Elation	0	0.67 ± 2.39	-1.97	0.055
Apathy/Indifference	4.70 ± 4.00	3.33 ± 3.83	1.478	0.144
Disinhibition	0.63 ± 2.06	0.90 ± 2.48	-0.479	0.634
Irritability/Lability	5.19 ± 4.61	4.73 ± 4.32	0.425	0.672
Aberrant motor behavior	4.52 ± 5.09	3.67 ± 4.10	0.741	0.463
Sleep/Night time behavior	3.07 ± 4.09	5.27 ± 3.66	-2.396	0.019*
Appetite/Eating change	0.74 ± 1.91	0.59 ± 1.63	0.358	0.721
NPI total score	33.23 ± 14.95	34.90 ± 17.71	-0.409	0.684

Notes: *p-value indicates significant within the two study groups (Independent-samples t- test); *$p < 0.05$; Abbreviation: NPI: Neuropsychiatric Inventory.

uate the relationship between several factors and behavioral symptoms of dementia, with adjustment for other potential confounding factors. A p-value of less than 0.05 was considered statistically significant. All of the statistical analyses were conducted using SPSS software package, version 22.0.

Result

Comparison of baseline information and NPI scores of associated BPSD in AD patients of different gender

A total of 76 patients of AD were included. There were 27 males and 49 females, who were aged 74.44 ± 9.88 and 75.06 ± 9.70 years old, respectively. There were no significant difference regarding age, years of education and course of disease between the males and females group (Table 1).

Statistical analysis showed that the scores of delusion, anxiety, and sleep behavior disorder were significantly higher in females than in males group ($p < 0.05$). The scores of the remaining 10 BPSD items were not significantly different (Table 1).

Comparison of baseline information and ADAS-cog scores in AD patients of different gender

Thirty two AD patients received ADAS-cog assessment, with 11 males and 21 females. Statistical analysis indicated that the scores of verbal ability attention and ADAS-cog total score were significantly higher in males than in females. There were no significant differences in cognitive assessment on the remaining 10 items (Table 2).

BPSD and WMH in AD patients

Score of periventricular hyperintensity (PV) WMH, deep subcortical (DW) WMH and total score of WMH were 2.00 ± 1.00, 1.07 ± 0.96, 3.07 ± 1.75 in the male group and 1.95 ± 0.90, 0.86 ± 0.71, 2.82 ± 1.26 in the female group. Independent samples t-test was conducted to compare the means of two groups, which found no significant difference ($p > 0.05$).

Our preliminary study showed that WMH of AD patients might be related with BPSD [7]. Depending on the Fazekas score, the patients were divided into two groups, namely, none to mild WMH group (0-2 points, n = 14) and moderate to severe WMH group (3-6 points, n = 23). NPI, CDR and ADAS-cog scores were compared between the two groups. The results showed that the NPI and CDR score were significantly different between the two groups, with the score being higher in the moderate to severe WMH group than in the none to mild WMH group ($P < 0.05$). No other significant differences were observed in the ADAS-cog scores of the remaining items ($p > 0.05$). It was thus inferred that severe WMH predicted more common BPSD (Table 3).

Table 2: Gender differences of ADAS-cog scores in AD patients.

ADAS-cog scores	Male Group (n = 27)	Female Group (n = 49)	*t*	*p*
Word recall	10.18 ± 4.05	8.62 ± 1.53	1.585	0.124
Naming objects	2.64 ± 1.75	1.48 ± 1.17	1.982	0.066
Commands	3.36 ± 1.36	2.43 ± 1.17	2.036	0.051
Constructional praxis	2.45 ± 1.57	1.90 ± 1.48	0.977	0.336
Ideational praxis	2.91 ± 1.64	1.76 ± 1.00	2.124	0.052
Orientation	5.30 ± 2.45	5.10 ± 2.05	0.244	0.809
Word recognition	10.36 ± 2.50	9.06 ± 3.18	1.178	0.248
Remembering instruction	4.09 ± 1.04	3.65 ± 1.39	0.918	0.366
Spoken language	2.64 ± 1.96	1.24 ± 1.22	2.154	0.049*
Word finding	2.45 ± 2.07	1.33 ± 1.20	1.659	0.12
Comprehension	2.27 ± 1.56	1.71 ± 1.23	1.114	0.274
Attention	2.64 ± 2.01	1.14 ± 1.24	2.248	0.041*
ADAS-cog total	50.36 ± 17.00	36.87 ± 14.46	2.361	0.025*

Notes: *p-value indicates significant within the two study groups (Independent-samples t- test); $p < 0.05$; Abbreviation: ADAS-cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale.

Table 3: Comparison of demographic data, NPI and ADAS-cog scores between Non-Mild WMH group and Moderate-Severe WMH group.

Parameter		Non-Mild WMH (n = 14)	Moderate-Severe WMH (n = 23)	X^2/t	df	*p*
Age(y)		71.28 ± 12.47	78.70 ± 6.10	-2.077[a]	16.854	0.053
Gender	Male	5	10	0.218	1	0.641
	Female	9	13			
Education(y)		7.00 ± 4.14	8.74 ± 5.28	-1.022	34	0.314
Course(m)		38.58 ± 23.48	52.57 ± 28.40	-1.445	31	0.159
CDR		1.68 ± 0.77	2.44 ± 0.51	-3.598	35	0.001*
NPI score		24.62 ± 12.55	41.39 ± 15.63	-3.308	34	0.002*
ADAS-cog score		36.43 ± 20.42	46.63 ± 15.53	-1.173	15	0.259

Notes: [a]Levene's Test for Equality of Variances (Age): F = 10.611, $p = 0.021$ ($p < 0.05$); *p-value indicates significant within the two study groups (Independent-samples t- test); **p-value indicates significant within the two study groups (Chi-square test). $p < 0.05$; Abbreviation: ADAS-cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; NPI: Neuropsychiatric Inventory; CDR: Clinical Dementia Rating Scale; WMH: Cerebral White Matter Hyperintensity; df: Degree of Freedom.

Table 4: Coefficients[a].

Model	Unstandardized Coefficients		Standardized Coefficients	t	*p*-value
	B	Std. Error	Beta		
(Constant)	20.976	6.45		3.252	0.003*
WMH	4.874	1.989	0.403	2.451	0.020*

[a]Dependent variable: NPI total score; *$p < 0.050$; Abbreviation: WMH: Total Score of White Matter Hyperintensity (Fazekas score).

Multiple linear stepwise regression analysis of NPI total scores

Furthermore we performed Multiple Linear Stepwise Regression Analysis. To examine the relationship between WMH, CDR, gender, course of disease and NPI total scores. The results showed that only WMH score entered the regression equation at last (t = 2.451, p = 0.020), while the other variables were removed from the equation, such as Gender (t = -0.315, p = 0.755), Course of disease (t = -0.679, p = 0.503), CDR (t = 0.809, p = 0.425). The result implied that only WMH score was independently associated with NPI total score. The important information of regression equation was in (Table 4).

Discussion

There is a new dementia patient every three seconds in the world. The economic and care burden of Alzheimer's disease has been increasing, and attention to AD is urgent and profound. A recent epidemiological study has shown that females are more likely to evolve into AD, while males are faced with a higher risk of vascular dementia [8]. Like age, gender is an important biological variable in the development and progression of AD. However, the existing studies seem to arrive at conflicting conclusions on the gender difference of BPSD in patients with AD [9].

The present study showed that delusion, anxiety and sleep behavior disorder were more frequent in females than in males AD patients. It inferred that the gender differences in etiology perhaps have significant effects on these symptoms of AD patients. Tatruru, et al. reported similar findings as ours, that is, males were less likely to suffer from delusional idea, hallucination, anxiety and emotional impairment [10]. Lowheim, et al. reported higher prevalence of aggressiveness in males, but more prevalent depressive symptoms in females [11]. Lee, et al. studied dementia patients from Korea, and found no significant gender difference in BPSD [12]. Delusion occurs more frequently in dementia patients, and the common types of delusion are delusion of being stolen, persecutory delusion, and delusion of jealousy. Studies have shown that polymorphism of the dopamine D2 receptor (DRD2) gene is associated with delusional symptom in dementia patients. DRD2-141C Ins/Ins genotype is related to various subtypes of delusion, including delusion of jealousy [13]. The prevalence of anxiety symptoms is 8%-71% in dementia patients [14]. It remains unclear whether anxiety reflects the degree of psychopathological symptoms of cognitive decline or whether the cognitive decline is caused by biological changes in the emotion-related neural circuit [15]. Sleep disorder may promote beta amyloid protein deposition in the brain and hence increase the risk of AD. Besides, degenerative change at the key sites of sleep regulatory pathway in AD is an important etiology of sleep disorder [16,17].

Our results also indicated gender differences in the scores of verbal ability, attention and ADAS-cog total score in AD patients, with females outperforming the males. Cognitive and non-cognitive disorders (mainly BPSD) constitute the clinical manifestations of dementia, and there may be gender differences in the prevalence, clinical manifestations, disease progression and prognosis. The identified risk factors for evolving into dementia in males are smoking, coronary heart disease, and cerebral trauma (with disturbance of consciousness); for female patients, the risk factors are longevity, female hormones, diabetes, overweight and hypertension. The shared risk factors are elderly age, family history of dementia, ApoE-ε4 carrier and low educational level [8].

Some studies have revealed gender differences in nucleus basalis of Meynert (NBM) existed. Cholinergic neurons in the frontal cortex are more active in females, while those in the hippocampus are more active in males [18]. The above evidences have implied the neurobiological basis for gender differences in BPSD in AD patients, and further studies are needed in this respect.

The etiology of BPSD is very complex and implicates neurobiological and social psychological factors. Our previous small sample-study has indicated that WMH severity may influence BPSD in patients with AD [7]. WMH, a radiological term that refers to white matter lesions of the brain, is also known as leukoaraiosis, which is considered relevant to the ischemic injury. As we know, course of disease, the severity of dementia and gender were also related to BPSD [9]. After regression analysis of all the aforementioned variables, our study showed that only WMH score still had significant impact on NPI total score. This result reminded us to pay attention to white matter lesion of Alzheimer's disease, especially for those patients with BPSD. Cerebral white matter is important constituent part of central nervous system, which is the area of nerve fibers aggregation. Several studies also support our opinions [19-21], while some studies reported the converse [22]. White matter lesions in AD usually occurs in periventricular and subcortical white matter. Periventricular white matter lesions may be related to cerebrospinal fluid circulation disorder, whereas subcortical white matter lesions are mainly caused by arteriolar sclerosis and tissue hypoxia. One study suggested that amyloid accumulation was associated with impaired structural integrity in WMHs putatively adding to effects of ischemia [23].

The present study had certain limitations, such as the sample size was small, and we used MRI technology for a rough qualitative study of cerebral white matter lesions,

but to further clarify the topic, the sample size should be increased in the future. Voxel-based morphometry (VBM) may be used for localization and quantitative study of white matter lesions.

Conclusion

Overall, our study confirmed that certain gender differences exist in behavioral and psychological symptoms of Alzheimer disease, such as delusion, anxiety and sleep behavior disorder, and cerebral white matter lesions were independently associated with behavioral and psychological symptoms of Alzheimer disease.

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