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Stage-Specific Gender Differences in Cognitive and Neuropsychiatric Manifestations of Vascular Dementia

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Abstract

Studies on gender differences in the clinical manifestations of vascular dementia (VaD) are still lacking. In the present study, gender comparisons of cognitive and neuropsychiatric profiles were conducted separately for mild and moderate-to-severe VaD in a total of 467 patients with VaD. There were no significant gender differences in cognitive manifestations, except that females performed better on immediate verbal recall than males in mild stage. Women were more likely to exhibit delusions (15.5% vs 7.4%), hallucinations (9.5% vs 3.4%), and depression (43.1% vs 27.3%) in mild stage. The predominance of male patients was observed in apathy at moderate-to-severe stage (50.5% vs 34.8%). To conclude, gender differences existed in neuropsychiatric symptoms of VaD and were especially pronounced in mild stage. Delusions, hallucinations, and depression were more prevalent in females in mild VaD, with the male predominance only in apathy in the later stage.

Keywords

vascular dementia, dementia stage, gender differences, neuropsychology, neuropsychiatry

Introduction

Gender differences are a common phenomenon and manifest in many ways, including cognitive, psychiatric, and behavioral characteristics. On average, healthy females have advantages on verbal tasks and healthy males have superior visuospatial functions.[1-3] It is widely accepted that the frequencies of depression and anxiety in the general population are higher in females than in males.[4,5] Based on these findings, researchers began to be interested in gender differences among patients with dementia. The studies were mainly focused on Alzheimer's disease (AD). Unlike healthy population, female patients with AD were reported to be equally or even more impaired than male patients on language functions and verbal memory,[6-9] and male and female patients performed similarly on visuospatial tasks.[10] Gender differences in neuropsychiatric symptoms, such as aggression,[11] apathy,[12] and delusions,[13] were also found in AD. Gender appears to play an important role in determining the frequencies and severities of psychiatric symptoms of AD, which then influence the treatment decisions.[14]

However, researches on gender specificities in vascular dementia (VaD) are quite limited. To our knowledge, only one study compared gender differences in cognitive impairments of VaD and showed women scored lower than men in the semantic memory task, while no gender differences were found in visuospatial ability.[10] There were no previous studies that assessed gender differences in neuropsychiatric symptoms of VaD. Given that the female predominance in depression and anxiety following stroke, the main cause of VaD, have been identified,[15,16] we hypothesized there would be gender-specific presentations in neuropsychiatric symptoms of VaD, which remained to be explored.

A large number of studies have investigated the mechanisms of gender differences in normal population, which are complex and probably associated with the interactions of social, physiological, metabolic, and hormonal factors. However, studies on

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gender differences in dementia are still insufficient, especially for VaD. A deeper understanding of the gender-specific clinical manifestations of VaD is helpful for further investigating the gender-specific pathogenic and progressive characteristics of VaD, and the gender differences in treatment choices and response.

In this study, we sought to determine gender differences in cognitive impairments, especially focusing on verbal memory and visuospatial ability, and neuropsychiatric symptoms among patients with VaD. Considering that previous studies suggested gender differences varied with dementia severity,[7,14] gender comparisons were made in different severities of VaD.

Methods

Participants

The present study is a part of China Cognition and Aging Study (China COAST), which is a longitudinal national study on the mild cognitive impairment (MCI) and dementia based on hospital and community population. All of our participants were selected from consecutive patients diagnosed with VaD in the baseline stage of the hospital-based part of China COAST, which lasted from September to December 2009 and conducted in multiple neurology clinics across China. The outpatients who satisfied any one of the following criteria were included to undergo cognitive screening in the China COAST: (1) 55 years or older, (2) complaint of cognitive impairment, and (3) history of cerebrovascular disease. The cognitive screening included Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Mini-Mental State Examination (MMSE), and a standardized diagnostic workup. Dementia was diagnosed based on *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition [*DSM-IV*]) criteria. For all our patients, VaD was a consensus diagnosis made by at least 2 experienced neurologists. These neurologists made the diagnosis strictly according to the criteria of the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) for probable VaD. All of our patients with VaD had focal signs on neurological examination and relevant brain imaging evidences (computed tomography [CT] or magnetic resonance imaging [MRI]), including multiple large vessel infarcts or a single strategically placed infarct, multiple basal ganglia and white matter lacunes, extensive periventricular white matter lesions, or combinations. There was a temporal relationship between cerebrovascular disease and dementia onset. The diagnosis of AD was made according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for probable AD in the China COAST. The imaging evidence of medial temporal lobe atrophy supported the diagnosis of AD. Patients with focal neurological deficits were excluded from AD. For the guarantee of the accuracy of the diagnosis, inter-rater reliability for each test and diagnosis was required to exceed .90 with videotaped interviews in the China COAST. Written informed consent was obtained from all participants or their relatives. This study was approved by the Institutional Review Board of Xuan Wu Hospital.

Assessments

All the participants in the present study underwent the following cognitive and neuropsychiatric assessments. Dementia severity was rated using the Clinical Dementia Rating scale (CDR), a 5-point scale (0, 0.5, 1, 2, and 3, normal to severe impairment).[17] Patients were classified into mild dementia (CDR 0.5, 1) and moderate-to-severe dementia (CDR 2, 3) according to the CDR scores. The World Health Organization–University of California–Los Angeles Auditory Verbal Learning Test (WHO-UCLA AVLT), which was thought to be applicable across cultures,[18,19] was used as a measure of verbal memory. In this test, the participants were asked to recall a 15-word list right after the presentation. This kind of immediate recall was repeated 3 times (maximum score = 45). Thirty minutes later, the participants completed the long delay free recall (maximum score = 15) and long delay recognition (maximum score = 15). In the current study, the Clock Drawing Test (CDT) was regarded as an indicator of visuospatial ability. The score ranged from 0 to 3—one point for drawing a correct clock shape, one point for writing all the 12 numbers with the right sequence and putting them in the right position, and one point for placing hands correctly.[20] For its simplicity and time saving, this scoring system was applied in China COAST. We used the Neuropsychiatric Inventory (NPI) to determine neuropsychiatric symptoms.[21] The scoring of NPI was based on the information from the caregivers. The NPI assesses the following symptoms: delusions, hallucinations, agitation/aggression, apathy, anxiety, depression, euphoria, irritability, disinhibition, aberrant motor behavior, sleep behavior disturbances, and appetite abnormalities. If a patient did not have any of these symptoms in the last month, the NPI was scored 0. If the answer was "yes," then the frequency (*occasionally*, 1; *often*, 2; *frequently*, 3; *very frequently*, 4) and severity (*mild*, 1; *moderate*, 2; *severe*, 3) were asked. The score of each symptom was calculated as the product of the frequency and severity.

Statistical Analysis

To summarize the demographic data of our patients, we used χ^2 tests for dichotomous variables and independent sample *t* tests for continuous data. We analyzed gender differences among patients with different dementia severities separately with similar analytic strategies. Multivariate analysis of variance (MANOVA) was used to examine the gender differences in cognitive functions; cognitive tests were analyzed as dependent variables simultaneously, with gender as independent variable and age, educational duration, and the use of anti-dementia drugs as covariates. Gender differences in the prevalence of

Table 1. Characteristics of Our Patients and Gender Comparisons of Cognitive Performances

	Mild dementia			Moderate-to-severe dementia		
	Male (n = 176)	Female (n = 116)	*P* value	Male (n = 109)	Female (n = 66)	*P* value
Age	66.09 (10.54)	65.81 (10.55)	.824	69.01 (10.06)	66.73 (10.62)	.156
Education (year)	8.05 (4.68)	4.41 (4.18)	<.001	7.96 (4.64)	4.82 (4.41)	<.001
Dementia family history[a]	14 (8.0)	4 (3.4)	.117	12 (11.0)	10 (15.2)	.423
Parkinsonism frequency[a]	10 (5.7)	6 (5.2)	.852	12 (11.0)	5 (7.6)	.457
Dementia drugs[a]	14 (8.0)	8 (6.9)	.737	15 (13.8)	8 (12.1)	.756
CDR						
Score = 1[a]	144 (81.8)	99 (85.3)	.430			
Score = 2[a]				93 (85.3)	51 (77.3)	.177
MMSE	17.72 (4.67)	15.92 (4.85)	.843	12.81 (5.99)	11.97 (5.07)	.388
WHO-UCLA AVLT						
Immediate recall	9.92 (4.83)	10.85 (4.87)	.014	6.83 (4.65)	6.26 (4.40)	.747
Delay recall	2.22 (2.28)	2.29 (2.34)	.498	1.10 (1.68)	0.92 (1.49)	.293
Recognition	5.36 (4.10)	5.43 (4.10)	.333	3.69 (3.57)	2.64 (3.56)	.499
CDT	1.35 (0.92)	1.25 (0.84)	.238	0.79 (0.65)	0.71 (0.72)	.133

Abbreviations: CDR, Clinical Dementia Rating scale; MMSE, Mini-Mental State Examination; WHO-UCLA AVLT, World Health Organization–University of California–Los Angeles Auditory Verbal Learning Test; CDT, Clock Drawing Test.
[a] Values are presented as numbers (percentages).

each NPI subscale (present, a score of 1 or higher; not present, a score of 0) were examined using χ^2 tests or Fisher exact tests if needed. The Mann-Whitney *U* tests were used to compare the total NPI score and each NPI item score between male and female patients. Subsequently, logistic regression analyses were performed to control for age and educational duration, with the individual symptoms as dependent variable and gender as independent variable. Furthermore, we adjusted for the use of anti-dementia and neuropsychiatric drugs and the parkinsonism, which may influence the neuropsychiatric symptoms.[22] *P* value <.05 was regarded as statistically significant.

Results

Patients' Characteristics

In the present study, there were 467 patients with VaD who completed all of the cognitive and neuropsychiatric assessments. The demographic data are given in Table 1. Male patients had a significantly higher education than female patients. In our participants, 26 male patients and 14 female patients had a family history for dementia. There were a total of 33 patients who had parkinsonism. There was no gender difference in parkinsonism frequency. Seeing that the China COAST was a large screening study, a majority of our patients underwent cognitive examinations for the first time, and only a small part of our patients had been diagnosed with VaD and received the anti-dementia drugs prior to our examinations. Among our participants, 45 patients were receiving anti-dementia drugs, and cholinesterase inhibitors were used in all of these patients. The prescription rate of neuropsychiatric drugs was low. Seven male patients and 4 female patients were receiving neuropsychiatric drugs, including selective serotonin reuptake inhibitors (SSRIs), olanzapine, and risperidone. The majority of patients with mild dementia had a CDR score of 1, and patients with moderate-to-severe dementia mainly had a CDR score of 2. There were no significant gender differences in the distribution of dementia severity.

Cognitive Tests

The results of gender comparisons of cognitive performances are presented in Table 1. The global cognitive function of men was comparable with that of women after controlling for age, educational duration, and the use of anti-dementia drugs. There were no significant gender differences in verbal memory and visuospatial ability, except that females performed better on immediate verbal recall than males in mild VaD.

Neuropsychiatric Symptoms

Table 2 shows the gender comparisons of the prevalence and scores of individual NPI symptoms. In mild VaD, 67% of male patients and 70.7% of female patients were reported by the caregivers to have at least one neuropsychiatric symptom. The prevalence and scores of delusions, hallucinations, and depression were significantly higher in women than in men. Furthermore, the prevalence of anxiety (25.0% compared to 16.5%) and sleep behavior behaviors (18.1% compared to 11.9%) was higher in females than males, but these differences did not reach significance.

With increasing dementia severity, 82.6% of men and 86.4% of women exhibited neuropsychiatric symptoms in moderate-to-severe VaD. The significant gender differences in neuropsychiatric symptoms among patients with moderate-to-severe VaD only existed in apathy, which was more prevalent in men (50.5% in men vs 34.8% in women, $P = .044$). After controlling for age and educational duration, logistic regression analyses produced the same pattern of results, with a higher risk of delusions (odds ratio [OR]: 2.30, 95%

Table 2. The Gender Comparisons of the Frequencies and Scores of Neuropsychiatric Symptoms[a]

	Mild dementia		Moderate-to-severe dementia	
NPI items	Male (n = 176)	Female (n = 116)	Male (n = 109)	Female (n = 66)
Delusions	7.4 (0.39 ± 1.79)	15.5 (0.78 ± 2.34) [bd]	18.3 (0.67 ± 1.93)	16.7 (0.80 ± 2.33)
Hallucinations	3.4 (0.16 ± 1.08)	9.5 (0.40 ± 1.74) [bd]	11.9 (0.38 ± 1.46)	18.2 (1.08 ± 2.78)
Agitation/aggression	18.8 (0.77 ± 2.00)	17.2 (0.59 ± 2.05)	33.9 (1.62 ± 3.13)	22.7 (1.32 ± 2.88)
Depression	27.3 (1.19 ± 2.55)	43.1 (1.86 ± 4.73) [cd]	36.7 (1.94 ± 3.67)	48.5 (2.88 ± 0.36)
Anxiety	16.5 (0.85 ± 2.39)	25.0 (0.93 ± 2.50)	27.5 (1.54 ± 3.43)	37.9 (2.26 ± 3.86)
Euphoria	4.5 (0.21 ± 1.27)	8.6 (0.28 ± 1.34)	7.3 (0.35 ± 1.46)	12.1 (0.42 ± 1.29)
Apathy	31.3 (1.87 ± 3.48)	31.0 (1.65 ± 3.22)	50.5 (3.79 ± 4.83)	34.8 (1.82 ± 3.26)[be]
Disinhibition	2.3 (0.09 ± 0.92)	5.2 (0.22 ± 1.25)	7.3 (0.44 ± 1.78)	9.1 (0.62 ± 2.16)
Irritability	12.5 (0.39 ± 1.45)	16.4 (0.45 ± 1.50)	19.3 (0.72 ± 2.11)	21.2 (1.05 ± 2.48)
Aberrant motor behavior	8.0 (0.35 ± 1.59)	11.2 (0.61 ± 2.34)	14.7 (0.94 ± 2.86)	24.2 (1.48 ± 3.14)
Sleep behavior disturbances	11.9 (0.74 ± 2.54)	18.1 (0.96 ± 2.57)	20.2 (1.29 ± 3.18)	22.7 (1.35 ± 2.77)
Appetite abnormalities	10.2 (0.27 ± 1.08)	8.6 (0.44 ± 1.88)	11.0 (0.54 ± 1.98)	15.2 (0.59 ± 1.74)
Total	67.0 (7.32 ± 9.33)	70.7 (9.16 ± 13.54)	82.6 (14.25 ± 15.03)	86.4 (15.65 ± 17.68)

Abbreviation: NPI, Neuropsychiatric Inventory.
[a] Data are expressed as percentages of patients with individual symptoms (means of scores ± SDs)
[b]/[c] Significant gender differences in the prevalence of NPI symptoms, χ^2 test: [b] *P* value <.05, [c] *P* value <.01.
[d]/[e] Significant gender differences in NPI scores, Mann-Whitney *U* test: [d] *P* value <.05, [e] *P* value <.01.

confidence interval [CI]: 1.08-4.91), hallucinations (OR: 2.97, 95%CI: 1.07-8.27), and depression (OR: 2.02, 95%CI: 1.23-3.31) in women than in men with mild VaD, and a higher risk of apathy (OR: 1.90, 95%CI: 1.01-3.58) in men than in women with moderate-to-severe VaD. Further adjustment for the parkinsonism and the use of anti-dementia and neuropsychiatric drugs did not change the results (in mild VaD: delusions, OR: 2.35, 95%CI: 1.10-5.03; hallucinations, OR: 2.89, 95%CI: 1.12-8.75; depression, OR: 2.10, 95%CI: 1.21-3.56; in moderate-to-severe VaD: apathy, OR: 1.89, 95%CI: 1.01-3.60).

Discussion

The results of the present study showed that there are gender differences in the presentation of VaD, which mainly exist in neuropsychiatric symptoms and are especially pronounced in mild stage. Female patients were more likely to exhibit delusions, hallucinations, and depression than male patients in mild VaD. Male patients were only more likely to exhibit apathy in moderate-to-severe VaD.

Usually in normal population, females have better verbal abilities and males have better visuospatial functions. Therefore, we hypothesized the gender differences in cognitive impairments of VaD are focus on verbal and visuospatial abilities. However, the results of this study did not entirely support our hypothesis. This study showed male and female patients with VaD had similar verbal and visuospatial functions, except that women could still maintain the female advantage in immediate verbal recall in the early stage of VaD. It is plausible that verbal memory ability has not been severely affected during early VaD.[23] As we mentioned, only one previous study conducted by Buckwalter has investigated gender differences in cognitive manifestations of VaD. They found that the average scores of female patients on the semantic memory test were lower than those of male patients with visuospatial ability showing no gender differences.[10] The study of both Buckwalter and ours demonstrated the female advantage in verbal memory and the male advantage in visuospatial ability were hardly to be found in VaD. This absence of gender differences in cognitive manifestations of VaD might be associated with gender differences in the patterns of cerebral organization. The greater bihemispheric representation in women than men during verbal memory task has been indicated,[24] whereas during visuospatial task males showed greater bilateral activity than females.[2] This gender-specific bilateral involvement may make verbal function of women and visuospatial ability of men more vulnerable to the neuropathological changes.[9,10] We hypothesized this gender difference in the patterns of cerebral organization might be one of the reasons that lead to the female advantage in verbal memory and the male advantage in visuospatial ability in normal population disappear among patients with VaD. Certainly, gender specificities in cognitive manifestations of VaD need to be confirmed by more studies, and the potential mechanisms deserve further investigation.

To our knowledge, no studies have investigated gender differences in neuropsychiatric symptoms of VaD. As a preliminary study, we found several neuropsychiatric symptoms were more prevalent in females with mild VaD, including delusions, hallucinations, and depression. The interactions of multiple factors, including social, pathological, metabolic, and hormonal, which are probably associated with the gender differences in neuropsychiatric symptoms, are very complex. For VaD, white matter (WM) lesions might be one of the factors. It has been reported that WM lesions, one of the clinical characteristics of VaD, are related to several neuropsychiatric symptoms, including delusions, hallucinations, and depression among patients with dementia.[25-27] Interestingly, gender may be a significant effect modifier of this relationship

between neuropsychiatric symptoms and WM lesions. A recent study showed depression was associated with WM hyperintensities among women, but not men, in a relatively healthy elderly population.[28] This gender difference in the susceptibility to WM lesions might contribute to the female predominance in depression in mild VaD in our study.

Neuropsychiatric symptoms have serious adverse consequences and deserve attention in the treatment of dementia. In AD, gender differences in the treatment of psychiatric and behavior symptoms have been demonstrated.[14] It seems that the gender differences in the frequency and severity of psychiatric problems are associated with the decision of treatment. Our results of gender differences in neuropsychiatric symptoms of VaD warrant further studies on gender specificities in the treatment. Considering that female patients with dementia were reported to be more likely to go untreated than male patients,[29] we suggest further attention to neuropsychiatric symptoms in female patients with VaD.

Strengths of the current study include the relatively large sample. All of our participants underwent a standardized diagnostic procedure. Gender differences were analyzed in different severities of dementia. However, there are some limitations in our study. Our participants were chosen from neurology outpatients and therefore were not representative of the general population, though our study results might be of value in clinical setting. Another limitation was the instruments we used. The CDT, like most other neuropsychological tasks, involves more than one single cognitive ability. However, the visuospatial function is necessary and important for the completion of CDT, which was used originally as a measure of visuospatial neglect. Although the NPI we used is a validated and widely used instrument, it relies on the information from caregivers instead of patients. The severity of symptoms assessed by the caregivers may be influenced by the caregivers' burden. In addition, it is likely to be difficult for the caregivers to distinguish depression and apathy. Furthermore, we conducted gender comparisons in different severities of dementia, while the cross-sectional study design precludes the assessments of gender differences in the evolution of cognitive impairments and neuropsychiatric symptoms.

In conclusion, our study shows gender differences exist in the clinical manifestations of VaD and are influenced by dementia severity. The results are of value in gender-specific analysis and treatment of VaD in clinical practice and have implications for further study of gender differences among patients with VaD. As a preliminary study, our results deserve further replication through cross-sectional studies using wider scales of cognitive assessments, and the progressions of cognitive and neuropsychiatric impairments in male and female patients need to be assessed by longitudinal follow-up.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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