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NEUROPSYCHIATRIC SYMPTOMS IN PATIENTS WITH VASCULAR DEMENTIA IN MAINLAND CHINA

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Abstract

Background: Neuropsychiatric deficits can induce marked disability in patients with dementia and increase caregiver distress. Several studies have found that neuropsychiatric symptoms are common both in patients with Alzheimer's disease (AD) and patients with vascular dementia (VaD). However, there are few studies of the neuropsychiatric disturbances in large clinical samples of patients with mixed (cortical - subcortical) VaD from mainland China. This study aimed to investigate the neuropsychiatric symptoms in VaD patients in mainland China. Methods: Eighty patients with mixed VaD for over 6 months duration, and their caregivers (VaD group), were recruited for interview in Zhongnan Hospital of Wuhan University, from June 2010 to June 2012. Eighty age- and sex-matched normal volunteers (control group) were interviewed at the same time. The Mini Mental State Examination (MMSE) and the Neuropsychiatric Inventory (NPI) were administered to the VaD patients, their caregivers, and normal volunteers. Group differences were analyzed using the unpaired t-test. Results: The total mean scores of the NPI in the VaD group were higher than in the control group ($P < 0.01$). The subscale scores of NPI, including delusions, hallucinations, depression, apathy, irritability, agitation, aberrant motor behavior, and change in appetite were significantly higher in the VaD group than in the control group ($P < 0.05$-0.01). Compared with the mild VaD subgroup, the NPI subscale scores of apathy, irritability and total scores were significantly higher in the moderate VaD subgroup ($P < 0.05$-0.01); the NPI subscale scores of anxiety, apathy, irritability, and total scores were significantly higher in the severe VaD subgroup ($P < 0.01$). Compared with the moderate VaD subgroup, the NPI subscale scores of anxiety and apathy were significantly higher in the severe VaD subgroup ($P < 0.05$-0.01). Conclusions: Neuropsychiatric symptoms, such as hallucination, anxiety, apathy, irritability and aberrant action behavior, are common in patients with mixed VaD from mainland China; anxiety and apathy were more pronounced in the subgroup of severe VaD patients.

Keywords

• Vascular dementia • Mini Mental State Examination • Neuropsychiatric Inventory • Neuropsychiatric symptoms

Introduction

Poststroke dementia occurs in up to one third of patients with clinically eloquent ischemic stroke after age 65 years [1]. Moreover, MRI-documented silent brain infarcts more than double the risk of dementia in the elderly [2]. In recent years, the concept of vascular cognitive impairment has been advanced as an alternative to the more narrowly construed notion of vascular dementia (VaD) [3], which confers an increased risk of death and institutionalization [4]. Neuropsychiatric symptoms can induce marked disability in patients with dementia and increase caregiver distress [5]. Several studies have found that neuropsychiatric symptoms are common both in patients with AD and with VaD [6-10]. Some studies suggested that neuropsychiatric symptoms were more common in VaD than in AD, but others report conflicting observations [7-9]. These discrepancies might be caused by different VaD diagnostic criteria with variable sensitivity and specificity, and use of different evaluation tools for neuropsychiatric manifestations [11-14]. The clinical presentation and course of these different subtypes of VaD vary but their neuropsychiatric manifestations have rarely been studied. Nevertheless, studies of neuropsychiatric disturbances in patients with VaD are few in mainland China. In this study, using a standard tool, the Neuropsychiatric Inventory (NPI), we examine and compare neuropsychiatric symptoms in patients with VaD in mainland China.

Methods

Participants

A large clinical sample of mixed (cortical-subcortical) VaD patients, with a duration of over 6 months, and normal control subjects, were evaluated by clinical interview, and neurological and physical examination at the Zhongnan Hospital, Wuhan University, from June 2010 to June 2012. The Mini Mental State Examination (MMSE) and the NPI were administered to the patients and caregivers, respectively. In this study, eighty patients with VaD (MMSE = 16.6 ± 7.8) were recruited as the VaD group; there were 39 males and 41 females aged from 52-78 years (average age 68.8 ± 8.8 years). The average educational level in the VaD group was 10.6 ± 4.5 years. Eighty normal volunteers (MMSE = 26.4 ± 3.2), who came to our hospital for a checkup and proved to be healthy, were also recruited in the same period as a control group for the study (40 males and 40 females aged from 53-76 years, average age 68.3 ± 9.2 years; average educational level 11.3 ± 4.6 years). Patients, family caregivers, and volunteers were given detailed information sheets and signed informed consent before answering the questionnaire. The study was carried out in accordance with the Declaration of Helsinki and approved by the institutional

review boards of the local Bioethics Committee of Zhongnan Hospital of Wuhan University.

Criteria for dementia

The inclusion criteria were age 50-80 years; history of stroke and neuroimaging (computed tomography or magnetic resonance imaging) showing evidence of ischemic stroke; cognitive impairment meeting the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for dementia; cognitive impairment deemed to have a vascular cause; a Hachinski Ischemic Score greater than 7 [15,16]; and a score of less than 12 on the Hamilton Depression Scale (HAMD for 17 items) [17]. Participants were excluded if they met the DSM-IV diagnostic criteria for depressive disorder [14,18]. Other exclusion criteria included heart failure, respiratory failure, other organ failure, pregnancy, or a tumor that could put the patient at special risk; a history of neurodegenerative diseases including Parkinson's disease, AD, multiple system atrophy, and Huntington's disease that could interfere with the efficacy evaluations; and inability to perform neuropsychological tests due to severe aphasia. We also excluded patients with cerebral hemorrhage or delirium. In addition, a serologic test for syphilis, folic acid, vitamin B12 and thyroxin levels were examined to exclude other causes of dementia.

Assessments and measures

The severity of cognitive status was assessed by the MMSE [17,19-21]. The MMSE is one of the most widely used screening instruments for dementia, and provides a total score ranging from 0 to 30, with lower scores indicative of greater cognitive impairment [22]. It was administered to the patients to obtain an overall level of current cognitive function. Subgroups of mild, moderate, and severe VaD were defined based on the MMSE points regarding educational background. The "mild VaD subgroup" refers to middle school or above with MMSE 20-23 points, primary school with MMSE 16-19 points, and illiterate with MMSE 13-15 points. The "moderate VaD subgroup" refers to middle school or above with MMSE 11-19 points, primary school with MMSE 8-15 points, and illiterate with MMSE 5-12 points.

The "severe VaD subgroup" refers to middle school or above with MMSE ≤ 10 points, primary school with MMSE ≤ 7 points, and illiterate with MMSE ≤ 4 points.

Information on neuropsychiatric symptoms was obtained from caregivers using the NPI [23], which was shown by Cummings *et al.* to be reliable and valid [24]. There is a screening question assaying each subarea, including delusions, hallucinations, agitation, apathy, anxiety, depression, euphoria, irritability, disinhibition, aberrant motor behavior, change in appetite, and nighttime behavior disturbances. If the answer to this screening question was "no", then no further questions were asked. If the answer was "yes", then subquestions were asked and ratings of the frequency and severity of the behavior were made by the caregiver based on scales with anchor points (frequency: 1 = occasionally, 2 = often, 3 = frequently, 4 = very frequently; severity: 1 = mild, 2 = moderate, 3 = severe). The frequency rating multiplied by the severity rating produced a composite score for each behavior. A global score for the NPI was generated by summing the total scores of the individual subscales. The Chinese version of NPI is a reliable and valid tool for measuring neuropsychiatric disturbances in patients with dementia [25,26].

Statistical analysis

The measurement data were expressed as mean ± standard deviation (SD). Group differences were analyzed using the unpaired t-test. All statistical analyses were performed with SPSS 11 (SPSS Inc., Chicago, IL, USA) for Windows operating system (Microsoft, Redmond, WA, USA) with a significance level set at $P < 0.05$.

Results

Demographic data and baseline characteristics between the two groups

There were no significant differences between the two groups with respect to sex, age, race, educational level and weight. The HAMD score in the VaD group (5.5 ± 4.2) was similar to that in the control group (5.6 ± 4.4, $P > 0.05$).

Comparison of the NPI subscale scores and total scores between the two groups

Table 1 shows the NPI mean scores in the VaD group and the control group. Total mean scores of the NPI in the VaD group were higher than that in the control group ($P < 0.01$). The subscale scores of NPI, including delusions, hallucinations, depression, apathy, irritability, agitation, aberrant motor behavior and change

Table 1. NPI subscale scores and total scores between two groups (mean ± SD).

	Control group	VaD group	P value
Delusions	0.00 ± 0.00	0.33 ± 1.48	< 0.01
Hallucinations	0.00 ± 0.00	0.33 ± 1.54	< 0.01
Depression	0.66 ± 1.63	2.28 ± 3.23	< 0.05
Anxiety	0.63 ± 1.41	1.54 ± 2.38	> 0.05
Apathy	0.21 ± 0.22	1.52 ± 2.49	< 0.01
Irritability	0.24 ± 0.82	0.86 ± 1.98	< 0.01
Euphoria	0.00 ± 0.00	0.58 ± 0.39	> 0.05
Agitation	0.00 ± 0.00	0.36 ± 1.66	< 0.05
Disinhibition	0.00 ± 0.00	0.17 ± 0.74	> 0.05
Aberrant motor behavior	0.00 ± 0.00	0.24 ± 0.78	< 0.05
Night time behavior disturbances	1.38 ± 2.24	1.43 ± 2.91	> 0.05
Change in appetite	0.16 ± 0.71	0.66 ± 2.13	< 0.05
Total scores	2.91 ± 4.69	8.82 ± 9.86	< 0.01

in appetite were significantly higher in the VaD group than those in the control group (*P* < 0.05-0.01). There was no significant difference between male and female patients in the VaD group with respect to NPI mean scores (data not shown).

Comparison of the NPI subscale scores and total scores between mild, moderate and severe VaD subgroups

Table 2 shows the NPI mean scores in the different VaD subgroups. Except disinhibition, aberrant motor behavior and nighttime behavior disturbances, the rest of the NPI subscale scores and total scores in the mild VaD subgroup were significantly higher than those in the control group (*P* < 0.05-0.01). Compared with the mild VaD subgroup, the NPI subscale scores of apathy, irritability, and total scores were significantly higher in the moderate VaD subgroup (*P* < 0.05-0.01), whereas the NPI subscale scores of anxiety, apathy, irritability and total scores were significantly higher in the severe VaD subgroup (*P* < 0.01). Compared with the moderate VaD subgroup, the NPI subscale scores of anxiety and apathy were significantly higher in the severe VaD subgroup (*P* < 0.05-0.01).

Discussion

Approximately 25% of patients remain demented 3 months after stroke. If selected cognitive dysfunctions are considered, 50-75% of stroke patients are affected [27]. In this study, we found the MMSE scores of VaD patients from mainland China to be significantly lower than in normal subjects (control group). Dementia is a syndrome consisting of several symptoms and hallmarked by a decline in cognition that leads to functional impairment, including a decline in memory, a decline in other cognitive abilities, a decline in emotional control or motivation, or a change in social behavior. The patient's awareness should be preserved, and the symptoms should be present for more than six months. Dementia is progressive and can be caused by several different diseases. The impact of dementia on quality of life, on caregiver burden, and on resource use is substantial [28,29]. Although the hallmark of dementia is cognitive decline, accompanying neuropsychiatric symptoms of dementia, such as apathy, depression, agitation, and delusion are prevalent. Neuropsychiatric symptoms are often more devastating and create more

discomfort for patients and their caregivers than do the cognitive deficits, and studies have shown an inverse relationship between neuropsychiatric symptoms, especially depression, and quality of life [30,31].

The NPI was introduced in 1994 by Cummings *et al*. [23] to assess dementia-related behavioral symptoms that they felt other measures did not sufficiently address. The NPI originally examined 10 subdomains of behavioral functioning: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behavior. Two more subdomains have been added since its development: nighttime behavioral disturbances and change in appetite [24]. This wide variety of domains means that, unlike other dementia measures, the NPI is able to screen for multiple types of dementia, not just AD. The NPI has been studied using samples of cognitively intact older adults. The fact that these individuals receive extremely low scores suggests that the NPI is good at distinguishing between healthy people and those with dementia. The NPI has become a standard instrument for clinical trials and other types of behavioral research in dementing disorders. The NPI was the subject of a workshop in Asia in conjunction with the International Workgroup on Dementia Drug Guidelines. Investigators using the NPI from 4 Asian areas (Taiwan, Hong Kong, Japan, and Thailand) presented conclusions from their research. A high prevalence of behavioral disturbances across Asian countries was found with rates comparable to those observed in Western countries. The NPI is a reliable and useful instrument to characterize behavioral changes in Asian and Western populations [32]. The NPI was first translated into Chinese in Hong Kong in 2001, with its concurrent validity, construct validity, and reliability validated in assessing the neuropsychiatric manifestations of dementia in the Chinese community [25]. Recently, the reliability and validity of the Chinese version of the NPI in patients with AD have been assessed in mainland China [26].

The prevalence and manifestations of neuropsychiatric disturbances in VaD and mixed AD/VaD have been well-recognized

Table 2. NPI subscale scores and total scores in different VaD subgroups (mean ± SD).

	Mild VaD subgroup	Moderate VaD subgroup	Severe VaD subgroup
Delusions	0.12 ± 0.68	0.44 ± 1.21	0.75 ± 2.77
Hallucinations	0.13 ± 0.44	0.25 ± 0.68	1.12 ± 2.38
Depression	1.90 ± 3.28	3.32 ± 3.54	1.84 ± 3.66
Anxiety	1.52 ± 2.45	2.24 ± 3.01	3.12 ± 1.78**###
Apathy	0.78 ± 1.88	1.87 ± 2.65**	3.88 ± 3.43**#
Irritability	0.46 ± 1.32	1.28 ± 1.56**	1.30 ± 2.90**
Euphoria	0.12 ± 0.44	0.00 ± 0.00	0.00 ± 0.00
Agitation	0.25 ± 1.04	0.00 ± 0.00	0.94 ± 2.96
Disinhibition	0.00 ± 0.00	0.00 ± 0.00	0.36 ± 1.44
Aberrant motor behavior	0.00 ± 0.32	0.11 ± 0.45	0.55 ± 1.54
Night time behavior disturbances	1.26 ± 2.89	1.78 ± 2.56	1.64 ± 3.89
Change in appetite	0.55 ± 2.11	0.38 ± 0.94	1.18 ± 3.26
Total scores	6.67 ± 7.88	10.92 ± 8.58*	14.04 ± 14.33**

Note: Compared with mild VaD subgroup, * P < 0.05, ** P < 0.01; compared with moderate VaD subgroup, # P < 0.05, ## P < 0.01

[33-36]. In a recent study of neuropsychiatric symptoms in Taiwanese patients with AD and VaD, the results showed a high prevalence of behavioral disturbances in both VaD and AD, and the symptoms profiles were similar in the AD, subcortical VaD, cortical VaD, and mixed cortical/subcortical VaD groups [36]. Some disturbances such as delusions, hallucination, agitation, and aberrant motor behavior were more common in advanced dementia [34,36]. The mean composite scores of the apathy and sleep disturbance domains in patients with cortical VaD were previously shown to be significantly higher than those in the patients with AD after controlling for years of education and MMSE score [36]. In this study, we found that total mean scores of the NPI in patients with mixed VaD from mainland China were higher than in the control group. The subscale scores of NPI, including delusions, hallucinations, depression, apathy, irritability, agitation, aberrant motor behavior and change in appetite were significantly higher in patients with mixed VaD from mainland China. We also found that anxiety and apathy were more obvious in severe VaD patients. Apathy has been attributed to disruption of corticosubcortical

circuits involving the basal ganglia, thalamus, and frontal lobes [37-39]. Cortical lesions in VaD likewise commonly involve frontal regions and may disrupt corticosubcortical circuits, whereas subcortical VaD disturbs corticosubcortical circuits through lacunar lesions and white matter ischemic injury [36].

In conclusion, the present study provides evidence of neuropsychiatric manifestations in a large mixed population of VaD patients, and shows that neuropsychiatric symptoms are common in patients with VaD from mainland China. The fact that neuropsychiatric symptoms as well as cognitive deficits can frequently arise from cerebrovascular diseases deserves attention, regardless of the development of dementia. As there is no standard treatment at present, identification and management of the vascular risk factors constitute the best policy of prevention and treatment of VaD with neuropsychiatric symptoms [40,41]. Caregiver intervention with group counseling and support would reduce behavioral and neuropsychiatric symptoms in the demented patients [42]. In Chinese culture, extended family support, acceptance of age-related cognitive changes,

and filial tradition of caring for elders may decrease caregiver burden and distress in the context of dementia. Several limitations need to be mentioned. First, because self-report questionnaires were used and verbally administered, the assumption was made that the subjects were truthful. Second, the group of the VaD patients and caregivers who agreed to participate in this study might not be representative of the entire group of the VaD patients and caregivers resulting in self-selection bias. Thus, caution must be taken in regards to generalizing results of this study to larger groups of Chinese patients with different types of VaD. Third, the instruments used in this study were developed in Western culture. Thus, cultural sensitivity of the instruments should be taken into account, even though they demonstrated good reliabilities.

Acknowledgments

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