Neuropsychiatric Manifestations in Vascular Cognitive Impairment Patients with and without Dementia

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Abstract-

Background: Neuropsychiatric profile has less been well recognized in all subtypes of vascular cognitive impairment (VCI). The aim of this study is to explore the neuropsychiatric manifestations in patients with different subtypes of VCI.

Methods: A consecutive series of 157 patients with VCI visited the dementia clinic in a regional hospital in mid-Taiwan were investigated in this study. All patients were examined with the Cognitive Abilities Screening Instrument (CASI), the Hachinski's Ischemic Scale (HIS), and the Clinical Dementia Rating (CDR) scale. The Neuropsychiatric Inventory (NPI) was used to assess neuropsychiatric symptoms.

Results: Of the 157 participants with VCI, 41 (26.1%) had VCI, without dementia (vascular CIND), 95 (60.5%) had vascular dementia (VaD), 21 (13.4%) had Alzheimer's disease (AD) with a vascular component (mixed AD/VaD). Sleep disturbance was the most common symptom in all patient groups. Apathy is significantly lower in VCI without dementia compared with VCI with dementia. Patients with VaD had the highest mean composite NPI scores in most domains and vascular CIND patients had the lowest composite scores in most domains.

Conclusions: Neuropsychiatric symptoms were common in patients with VCI with and without dementia. It deserves attention that neuropsychiatric symptoms as well as cognitive deficits frequently arise from cerebrovascular disease regardless of the development of dementia.

Key Words: Alzheimer's disease with a vascular component, Neuropsychiatric, Vascular cognitive impairment, Vascular dementia

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INTRODUCTION

Vascular cognitive impairment (VCI) is a relatively new concept which describes individuals with significant cognitive difficulties that arise from cerebrovascular disease and ischemic brain injury[(1)]. Cerebrovascular disease is one of the major risk factors for cognitive impairment. Approximately one-quarter of patients

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remain demented 3 months after a stroke. If selected cognitive dysfunctions are considered, 50-75% of stroke patients are found to be affected[2]. In recent years, the concept of VCI has been advanced as an alternative to the more narrowly construed notion of VaD[1]. In the Canadian Study of Health and Aging (CSHA), 3 clinical subtypes of VCI are proposed which include patients with vascular dementia (VaD), patients with mixed vascular and degenerative dementias (mixed AD/VaD), as well as patients with cognitive impairment of vascular origin who do not meet the traditional dementia criteria (vascular cognitive impairment, no dementia, vascular CIND)[3-5]. VCI is common (prevalence of 5% in those aged 65 years and older) and that all subtypes of VCI confer an increased risk of death and institutionalization[5]. Although many studies have investigated the neuropsychiatric symptoms in patients with VaD as well as patients with mixed AD/VaD, there are few data concerned these symptoms in patients with vascular CIND. Therefore, the purpose of the current study is to examine and to compare the neuropsychiatric symptoms in patients with vascular CIND, VaD, and mixed AD/VaD.

METHODS

The study was conducted in a dementia clinic in a 500-bed regional hospital in mid-Taiwan. A consecutive series of 157 patients with VCI were enrolled in this study. The VaD patients were diagnosed according to the criteria in the fourth edition of the Diagnostic and Statistic Manual of Mental Disorders (DSM-IV) which require focal neurological signs and symptoms or laboratory evidence for cerebrovascular disease. They also require multiple cognitive deficits manifested by both impaired memory and at least one of apraxia, agnosia, aphasia, or disturbance in executive functions. Deficits must represent a decline from a previous level, must lead to substantial impairment in social or occupational functioning, and must not occur exclusively during the course of a delirium. The diagnosis of mixed AD/VaD was made in one of the two situations. In the first, an elderly patient may meet criteria for dementia, marked by primary memory complaints and a slow insidious course consistent with Alzheimer's disease. No history of frank stroke or focal findings on neurological examination is present. However, neuroimaging shows extensive, diffuse white matter hyperintensities (WMHs) and/or the presence of multiple subcortical lacunar infarction, and the patient reports many risk factors for stroke such as hypertension, diabetes mellitus, or dyslipidemia. In the second, a patient with a history of stroke-related dementia shows continuous insidious decline without concomitant change in cerebrovascular disease burden. The diagnosis of vascular CIND was based on evidence of cognitive impairment from the clinical examination, Clinical Dementia Rating (CDR) scale 0.5 and a full score of Cognitive Abilities Screening Instrument (CASI) higher than the cutoff point of dementia. The norms for CASI were obtained from a large-scale community study in which the subjects were stratified into nine subgroups; three aforementioned education levels by three age levels, less than 69 years, between 70-79, and more than 80[6]. It is also necessary to identify significantly related vascular features which require focal neurological signs and symptoms or laboratory evidence for cerebrovascular disease. The cognitive impairments in vascular CIND were not sufficiently severe to interfere with social or occupational functioning.

All patients received screening tests using CASI and the Hachinski's Ischemic Scale (HIS). The majority of patients (66.7%) had a brain CT or MRI scan. They also underwent extensive laboratory tests to rule out other possible causes of dementia. The severity of dementia was acquired using the CDR scale and sum of boxes of CDR (CDR-SB). We used the 12-item version of the Neuropsychiatric Inventory (NPI) that divided mental/behavioral phenomena into 12 domains on the basis of observations within the past month. All of the 12 NPI domains were rated on symptom frequency from 1 (occasionally) to 4 (very frequently), on symptom severity from 1 (mild) to 3 (severe), and on caregiver burden from 0 (none) to 5 (extremely).

The means of the variables of demographical, neuropsychological data, subscale (frequency x severity) and caregiver burden in each domain of NPI, and the

composite score of NPI were analyzed using one way analysis of variance (ANOVA). The Scheffe test was used to explore the individual group effects. The significance of group differences in frequencies of neuropsychiatric symptoms was checked by the χ^2 test.

RESULTS

A total of 157 consecutive patients participated in this study (63 female and 94 male, with a mean age of 71.0 years, S.D. 10.4 years). Their mean length of education was 6.3 years (SD, 4.7 years, ranging from 0 to 19 years). The mean score of HIS was 8.2 (SD, 2.7). Among them, 41 (26.1%) had vascular CIND, 95 (60.5%) had VaD, whereas 21 (13.4%) had mixed AD/VaD. The comparison among vascular CIND, VaD, and mixed AD/VaD groups showed that there were no significantly differences in age (p=0.095). The CDR stage (p<0.001), CDR-SB (p<0.001), MMSE (p<0.001), and CASI (p<0.001) were higher in vascular CIND group compared with VaD or mixed AD/VaD groups. The HIS (p<0.001) was significantly higher in VaD group compared with vascular CIND and mixed AD/VaD groups (Table 1). The correlation of the HIS and the sum of composite scores in 12 domains of NPI showed a significant correlation (r=0.342, p<0.001).

In all participants, the frequency of any symptom in NPI was 90%. Sleep disturbance was the most common symptom (61%), followed by depression (46%), apathy (44%), irritability (39%), anxiety (30%), appetite/eating (28%), agitation (27%), delusion (22%), hallucination (22%), aberrant motor behavior (20%), disinhibition (11%), and euphoria (4%). The overall frequency of neuropsychiatric symptoms did not differ among the three groups (85% v 92% and 90%, p=0.546). The frequencies of hallucinations (p=0.002), apathy (p=0.007), disinhibition (p=0.040) and aberrant motor behaviour (p=0.005) were significantly different among three groups (Table 2).

Post-hoc Scheffe's test of the individual group effects showed that the composite (frequency x severity) scores of hallucination, agitation, and aberrant motor behaviour were lower in vascular CIND group compared with VaD group whereas that of apathy was lower in vascular CIND group compared with VaD and mixed AD/VaD groups. The sum of composite scores in 12 domains of NPI (p=0.002) was significantly lower in vascular CIND group (Table 3).

For the purpose of exploring the correlations of neuropsychiatric symptoms and stroke localization in vascular CIND, we analyzed the stroke lesions of our vascular CIND patients. All of our vascular CIND cases have stroke either according to the clinical history or the brain imaging study. Thirty four had performed at least one brain CT or MRI and only 24 patients had stroke lesions shown in their CT or MRI scans. Because the total num-

Table 1. *The demographic data and neuropsychological findings*

	VCIND (n=41)	VaD (n=95)	Mixed (n=21)	p-value
Age, mean years (S.D.)	69.5 (10.1)	70.7 (10.2)	75.4 (9.8)	0.095
Sex, m/f	27/14	55/40	12/9	0.665
Education, mean years (S.D.)	8.1 (4.3)	6.2 (4.9)	3.5 (3.0)	0.001
MMSE (S.D.)	25.7 (3.5)	15.1 (7.6)	11.4 (4.1)	< 0.001
CASI (S.D.)	80.6 (10.1)	46.5 (24.9)	33.8 (19.2)	< 0.001
CDR (S.D.)	0.5 (0.0)	1.4 (0.8)	1.7 (0.8)	< 0.001
CDR-SB (S.D.)	2.7 (1.2)	8.2 (4.2)	10.1 (4.1)	< 0.001
HIS (S.D.)	6.8 (2.4)	9.1 (2.4)	6.6 (2.9)	< 0.001

The means of the variables of demographical and neuropsychological data were analyzed using one way ANOVA; VCIND: vascular cognitive impairment, no dementia; VaD: vascular dementia; Mixed: mixed Alzheimer's disease and vascular dementia; MMSE: Mini Mental State Examination; CASI: Cognitive Abilities Screening Instrument; CDR: Clinical Dementia Rating scale; CDR-SB: Sum of boxes of CDR; HIS: Hachinski's Ischemic Scale.

ber of our vascular CIND cases that had lesions in imaging studies is small (n=24) and the lesion sites were varied, we simply divided them into two groups: cortical (n=10) and subcortical (n=14) groups. The sum of composite scores in 12 domains of NPI (p=0.966) did not show significant difference between two groups. We further analyzed our cortical group cases and found most of them have lesions located on the temporal or parietal lobes and only one patient has a frontal lobe lesion. Among our subcortical group cases, most of them have lesions located on the basal ganglia or thalamus and only one patient has a frontal white matter lesion. No mixed cortical/subcortical case was found in our vascular CIND series.

Table 2. *Percentage frequency of Neuropsychiatric Inventory disturbances in patients with different types VCI*

	VCIND (n=41)	VaD (n=95)	Mixed (n=21)	p-value
Delusions	17	26	14	0.317
Hallucinations	2	28	29	0.002
Agitation	12	32	33	0.050
Depression	41	49	33	0.650
Anxiety	29	32	24	0.777
Euphoria	2	6	0	0.345
Apathy	24	48	62	0.007
Disinhibition	5	16	0	0.040
Irritability	34	41	38	0.749
Aberrant motor behaviour	2	26	29	0.004
Sleep	59	60	67	0.816
Appetite/eating	24	31	24	0.690
Any symptoms	85	92	90	0.546

The significance of group differences in frequencies of neuropsychiatric symptoms was checked by the χ^2 test; VCIND: vascular cognitive impairment, no dementia; VaD: vascular dementia; Mixed: mixed Alzheimer's disease and vascular dementia.

Table 3. *Neuropsychiatric Inventory (NPI) subscale scores, sum of scores, and caregiver burden scores in patients with different types VCI*

	VCIND (n=41)	VaD (n=95)	Mixed (n=21)	p-value	Post-hoc comparisons
Delusions	0.7 (1.8)	1.7 (3.6)	1.0 (2.9)	0.189	—
Hallucinations	0.0 (0.2)	1.6 (3.5)	1.4 (3.1)	0.014	VaD > VCIND
Agitation	0.5 (1.6)	2.1 (3.8)	1.5 (3.0)	0.030	VaD > VCIND
Depression	1.4 (2.5)	2.8 (4.0)	2.2 (4.0)	0.149	—
Anxiety	0.9 (1.9)	1.9 (3.6)	1.0 (2.2)	0.132	—
Euphoria	0.1 (0.3)	0.4 (1.6)	0.0 (0.0)	0.225	—
Apathy	1.7 (3.7)	4.6 (5.3)	6.0 (5.5)	0.001	VaD = Mixed > VCIND
Disinhibition	0.3 (1.9)	0.9 (2.5)	0.0 (0.0)	0.152	—
Irritability	1.3 (2.6)	2.9 (4.3)	2.4 (3.9)	0.087	—
Aberrant motor behaviour	0.2 (1.3)	2.3 (4.4)	1.7 (3.9)	0.011	VaD > VCIND
Sleep	5.1 (5.4)	5.2 (5.1)	5.2 (5.1)	0.982	—
Appetite/eating	1.7 (3.4)	2.5 (4.1)	1.9 (3.9)	0.488	—
NPI-sum	13.5 (11.6)	27.7 (22.2)	23.5 (21.5)	0.002	VaD = Mixed > VCIND
NPI-burden	4.2 (4.5)	8.9 (7.7)	8.2 (9.8)	0.003	VaD = Mixed > VCIND

The means of subscale (frequency × severity) and caregiver burden in each domain of NPI, and the composite score of NPI were analyzed using one way ANOVA; VCIND: vascular cognitive impairment, no dementia; VaD: vascular dementia; Mixed: mixed Alzheimer's disease and vascular dementia; NPI-sum: sum of 12 domains in NPI (frequency × severity); NPI-burden: sum of caregiver burden in 12 domains in NPI; Post-hoc multiple comparisons by Scheffe's test.

DISCUSSION

Our study showed neuropsychiatric symptoms are very common in patients with VCI and the frequency of any symptom in NPI was up to 90% in all participants. Sleep disturbances (61%), depression (46%), and apathy (44%) were the first three common symptoms. Frequency and severity of delusion is similar in 3 groups. Apathy was significantly lower in vascular CIND group compared with the other two groups. Hallucination, agitation, and aberrant motor behaviour were significantly lower in vascular CIND group compared with VaD group. Although frequency and severity of some neuropsychiatric symptoms were lower in vascular CIND, the overall frequency of any symptom in NPI in this group is still high (85%). We would like to highlight our findings in patients with vascular CIND in whom the neuropsychiatric profile has less been well recognized in previous studies[3-5]. Although the sum of composite scores in 12 domains and the sum of caregiver burden in NPI were significantly lower in vascular CIND group compared with VaD and mixed AD/VaD groups, the overall frequency of neuropsychiatric symptoms did not differ from that of the other 2 groups (85% v 92% and 90%, p=0.546). In vascular CIND, sleep disturbances (59%), depression (41%), and irritability (34%) are the three most common behvaioural symptoms. Apathy is relatively less common in vascular CIND (24% v 48% and 62%, p=0.007) and has a lower composite score (1.7 (3.7) v 4.6 (5.3) and 6.0 (5.5), p=0.001) compared with the other two groups.

The prevalence and manifestations of neuropsychiatric disturbances in VaD and mixed AD/VaD are well recognized in many studies[7-10]. In a most recent study of neuropsychiatric symptoms in Taiwanese patients with AD and VaD, the results showed a high prevalence of behavioural 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[10]. Some disturbances such as delusions, hallucination, agitation, and aberrant motor activities were more common in advanced dementia[8,10]. Findings in our study support this observation.

VCI is a relatively new concept to substitute the concept of multi-infarct dementia (MID) or vascular dementia (VaD). Cerebrovascular disease is one of the major risk factors for cognitive impairment as well as neuropsychiatric disturbances. Compared with traditional notion of multi-infarct dementia or vascular dementia, the value added by the concept of VCI arises chiefly from its greater inclusiveness in estimating the vascular burden of cognitive illness[11]. Roman et al.[12] indicated that the concept of VCI could be more useful if it were to be limited to cases of vascular MCI without dementia, by analogy with the concept of amnestic MCI. The CSHA group successfully implemented a restricted definition of VCI, excluding cases of dementia (vascular CIND)[3-5]. Therefore, we use the CSHA criteria and the CDR stage 0.5 for the diagnosis of vascular CIND in this study and we propose vascular CIND and vascular MCI being the same concept. Studies in cognitive impairment or dementia in patients with cerebral vascular insults disclose that impaired executive and visuospatial functions are typical features. In this study, we use the Chinese version of CASI for screening and evaluation of the cognitive functions and several domains in CASI may be considered as part of the executive functions, i.e., domains of attention, abstract thinking, mental manipulation and verbal fluency. Fifty six percent (23/41) of our vascular CIND patients showed impairment in at least one of these domains. We also compare the presentation of neuropsychological patterns and that of NPI and we are not able to find significant correlation of the neuropsychological pattern with the NPI scores.

There is a varied etiology of VCI which can be broadly broken down into large vessel pathology, small vessel pathology, and post-ischemic encephalopathies[13-15]. Other pathologies such as hemorrhagic strokes as well as genetic factors can contribute to VCI. As the various etiology of VCI, the clinical presentation and the cognitive deficit in VCI is likely to be heterogeneous that may depend on the number, size, and locations of the infarcts[16,17]. In this study, the NPI did not show correlation with stroke localization, however, we must emphasize that the cases number of our vascular CIND group is small and further studies are necessary to

explore this correlation.

Finally, there may be two probabilities for the finding of positive correlation between HIS and NPI in this study. First, some of the symptoms in HIS and NPI are similar or overlapping, i.e., depression, somatic complaints, and emotional incontinence. Second, the severity of NPI may go along with the increasing numbers of vascular risk factors. Since there is no standard treatment at present, identification and management of the vascular risk factors is the best policy of prevention and treatment of VCI[18].

In conclusion, the present study provides the findings in neuropsychiatric manifestations of vascular CIND and shows that neuropsychiatric symptoms are common in patients with VCI. It deserves attention that neuropsychiatric symptoms as well as cognitive deficits can frequently arise from cerebrovascular diseases, regardless of the development of dementia.

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