

Neuropsychiatric profiles in patients with Alzheimer's disease and vascular dementia

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J Neurol Neurosurg Psychiatry 2005;76:1337–1341. doi: 10.1136/jnnp.2004.056408

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Received 14 October 2004
In revised form
16 January 2005
Accepted 26 January 2005

Objective: To explore the neuropsychiatric manifestations in patients with Alzheimer's disease (AD) and cortical and subcortical vascular dementia (VaD).

Methods: We investigated consecutive patients with dementia. All the participants received brain computed tomography. The diagnosis of dementia was confirmed by clinical criteria and the imaging findings. Only patients with probable AD, and subcortical and cortical VaD were included. The Mini Mental State Examination (MMSE) was used to evaluate global cognitive function, and the Neuropsychiatric Inventory (NPI) was used to assess neuropsychiatric symptoms.

Results: Of the 536 participants with dementia, 320 (59.7%) had AD, 161 (30%) had subcortical VaD, 35 (6.4%) had cortical VaD, and 16 (2.9%) had mixed cortical and subcortical VaD. Cortical VaD patients had the highest mean composite NPI scores in all domains and AD patients had the lowest composite scores in most domains. The mean composite scores of the apathy and sleep disturbance domains in patients with cortical VaD were significantly higher than those in the patients with AD after controlling for years of education and MMSE score ($p < 0.01$).

Conclusions: There were few differences among the patients with AD, subcortical VaD and cortical VaD. The most consistent differences were the high sleep disturbance scores in those with cortical VaD.

Neuropsychiatric symptoms can induce marked disability in patients with dementia and increase caregiver distress.¹ Several studies have found that neuropsychiatric symptoms are common both in patients with Alzheimer's disease (AD) and those with vascular dementia (VaD).^{2–6} Nevertheless, studies of the neuropsychiatric disturbances in patients with VaD are few and the results are controversial. Some studies suggested that neuropsychiatric symptoms were more common in VaD than in AD, but others report conflicting observations.^{2–4} Investigations of affective disorder also revealed controversial findings between the patients with VaD and AD.^{2–3} These discrepancies might be caused by different VaD diagnostic criteria with variable sensitivity and specificity,^{7–10} and use of different evaluation tools for neuropsychiatric manifestations.

The association between AD and VaD is complex. It is not uncommon to have vascular changes in patients with AD, and the vascular lesions can worsen cognitive impairment.^{11–13} Nevertheless, the clinical cognitive profiles of AD and VaD are distinguishable, as frontal executive dysfunction is the most prominent feature of VaD.¹⁴ Could different types of dementia also present different neuropsychiatric profiles? This question is important because these differences could affect treatment approaches and caregiver distress.^{6–15}

The neuropathology of VaD is heterogeneous. Several vascular pathologies can lead to dementia.¹⁶ The clinical presentation and course of these different subtypes of VaD vary but their neuropsychiatric manifestations have rarely been studied. A syndrome of subcortical VaD incorporating both "Binswanger's disease" and "lacunar state" is a more homogenous group.¹⁷ To subgroup VaD into subcortical and cortical types may facilitate comparisons between AD and VaD.

In this study, we assessed neuropsychiatric symptoms using a standard tool, the Neuropsychiatric Inventory (NPI),¹⁸ in a large clinical sample of consecutive patients with AD and different subtypes of VaD. The aim of this study was to

determine if the neuropsychiatric manifestations in patients with AD, cortical VaD, and subcortical VaD differ.

PATIENTS AND METHODS

Patients

The study comprised 1376 consecutive outpatients who complained of memory decline and were examined at the outpatient clinic of the Taipei Veterans General Hospital from December 1999 to October 2003. The Institutional review board of Taipei Veterans General Hospital approved the study protocol.

Assessments and measures

All patients were evaluated by clinical interview, and neurological and physical examination. The Mini Mental State Examination (MMSE)¹⁹ and NPI¹⁸ were administered to the patients and caregivers respectively.

The MMSE¹⁹ 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. It was administered to the patients to obtain an overall level of current cognitive function.

Information on neuropsychiatric symptoms was obtained from caregivers using the NPI.¹⁸ There is a screening question assaying each sub-area, including delusions, hallucinations, agitation, apathy, anxiety, depression, euphoria, irritability, disinhibition, aberrant motor behaviour, change in appetite, and night time behaviour disturbances. If the answer to this screening question was "no", then no further questions were asked. If the answer was "yes", then sub-questions were asked and ratings of the frequency and severity of the

Abbreviations: AD, Alzheimer's disease; CDR, Clinical Dementia Rating; CT, computed tomography; CVD, cerebrovascular diseases; DSM-IV, *Diagnostic and statistical manual of mental disorders*, 4th edition; MMSE, Mini Mental State Examination; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; NPI, Neuropsychiatric Inventory; VaD, vascular dementia

behaviour 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 behaviour. A global score for the NPI was generated by summing the total scores of the individual subscales. Cronbach's α for overall reliability of NPI was 0.88 and the concurrent validity was good, as shown by an acceptable correlation between NPI scores and other validated measurements.¹⁸

The Clinical Dementia Rating (CDR) scale provides a global rating of the severity of dementia, ranging from 0 (no impairment) to 3 (severe impairment).²⁰ The overall CDR rating was obtained from one primary domain (memory) and five secondary domains (orientation, judgement and problem solving, community affairs, home hobbies, and personal care).

We reviewed the relevant medical records and requested laboratory tests for participants with dementia, including complete blood counts, chemistries, serum vitamin B12, folic acid, thyroid function tests, and syphilis serology. Brain computerised tomography (CT) was also obtained on all participants with dementia.

Criteria of dementia

The diagnosis of dementia was made according to the *Diagnostic and statistical manual of mental disorders*, 4th edition (DSM-IV) criteria.²¹ Patients with delirium were excluded.

Subjects who met the dementia criteria were further classified as to their type of dementia at a consensus meeting after the history, laboratory findings, and the results of brain CT were reviewed. The diagnostic physicians were blinded to the results of the NPI.

Patients were diagnosed as having AD if they met the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) guidelines.²² Patients who fulfilled NINCDS-ADRDA²³ criteria for probable AD and had a single "silent" lacune, small cortical infarct, or disproportionately large ventricles found on brain imaging were excluded from analysis in this study.

VaD was defined according to modified DSM-IV criteria.²¹ DSM-IV criteria²¹ for VaD originally allowed focal neurological signs or laboratory evidence indicative of cerebrovascular disease (CVD). However, in this study, we required both the clinical criteria and demonstrate ischaemic abnormalities on CT. We classified VaD based on CT findings as subcortical VaD (small vessel disease, multiple lacunar infarcts, and/or extensive periventricular white matter lesions) and cortical VaD (large vessel disease, infarcts involving the cortical grey matter). We excluded patients with cerebral haemorrhage.

Statistical analysis

Statistical analysis was performed with SPSS for Windows (version 11.0.; SPSS Inc., Chicago, IL, USA) We used the χ^2 test to compare the proportions of participants with different types of dementia who had a score of 1 or higher in any individual NPI domain. We also compared the prevalence of neuropsychiatric disturbances in different dementia stages. We compared the NPI mean scores for participants with AD, subcortical VaD, cortical VaD, and mixed cortical and subcortical VaD as an indicator of behavioural change in each domain. The differences between the groups were analysed using one way analysis of variance, and the Scheffé test was used to explore the individual group effects.

To control for the severity of dementia as a confounding factor, we constructed a series of linear regression models, one for each domain and one for the total NPI score. Individual NPI domain scores or the NPI total score were the

dependent variables, and the presence or absence of different types of dementia was the independent variable. We also adjusted for MMSE and educational level in the analysis. A p value <0.01 was regarded as statically significant, balancing the risk of type I and II errors.

RESULTS

Patients' characteristics

Fig 1 shows a flow diagram describing the number of participants participating to the study and those meeting inclusion and exclusion criteria. A total 536 subjects participated in this study: 320 (59.7%) with AD (mean (SD) age 75.2 (7.2) years), 161 (30%) with subcortical VaD (75.1 (7.3) years), 35 (6.4%) with cortical VaD (75.8 (6.9) years), and 16 (2.9%) with mixed cortical and subcortical VaD (74.0 (7.0) years). The proportion of male patients was significantly lower in the AD compared with the subcortical VaD group (54% v 69%, $p<0.01$) and the proportion of severe dementia (CDR = 3) was significantly lower in the AD compared with the cortical VaD group (8% v 29%, $p<0.001$). The age, educational level, and MMSE score did not differ between the subjects with solely cortical and with mixed cortical and subcortical lesions. The patients with solely cortical VaD had significantly lower mean (SD) MMSE scores compared with AD or solely subcortical VaD patients (11.6 (7.5) v 17.1 (6.8) and 15.6 (6.8), $p<0.001$).

Neuropsychiatric manifestations among the different types of dementia

Fig 2 compares the prevalence of NPI based disturbances in participants with AD and those with subcortical, cortical, and mixed VaD. The prevalence of NPI disturbances was similar in the four groups. The patients with cortical VaD had marginally greater prevalence of agitation and sleep disturbances ($p = 0.03$ and 0.04 , respectively).

Comparing the mean composite subcores of the NPI domains across the four types of dementia, the cortical VaD had the highest composite scores in all domains and the highest total NPI score. The total 12 item NPI score reached significance by one way analysis of variance ($p<0.01$) but showed only a trend toward a difference between AD and cortical VaD by the Scheffé test (mean (SD) 13.8 (17.9) v 24.6 (27.3), $p = 0.02$). Among the subdomains, only the apathy and sleep disturbance domains reached statistical significance by one way analysis of variance ($p<0.01$). Comparisons using the Scheffé test indicated that the cortical VaD group had significantly higher scores compared with the AD group in the sleep disturbance domain (3.6 (4.1) v 1.7 (2.8), $p<0.01$), and there was a trend for patients with cortical VaD and subcortical VaD to have higher scores compared with the AD group in the apathy domain (3.4 (3.9) and 2.6 (3.8) v 1.6 (2.8), $p = 0.03$).

Relationship of severity of dementia to the neuropsychiatric manifestations

Table 1 shows the prevalence of individual NPI domain scores in patients with dementia of different severities as classified by the CDR. We did not include mixed VaD during the analysis because of the small number of patients. The prevalence of delusions, hallucinations, and aberrant motor activities increased significantly with the severity of dementia in patients with AD and subcortical VaD. The differences were statistically significant for the prevalence of apathy, agitation, and disinhibition in patients with AD. The prevalence of sleep disturbance was different in the patients with subcortical VaD. There were no differences in the prevalence of any NPI domain except the apathy domain across CDR staging in patients with cortical VaD. In patients with mild dementia (CDR = 1), there were no differences in

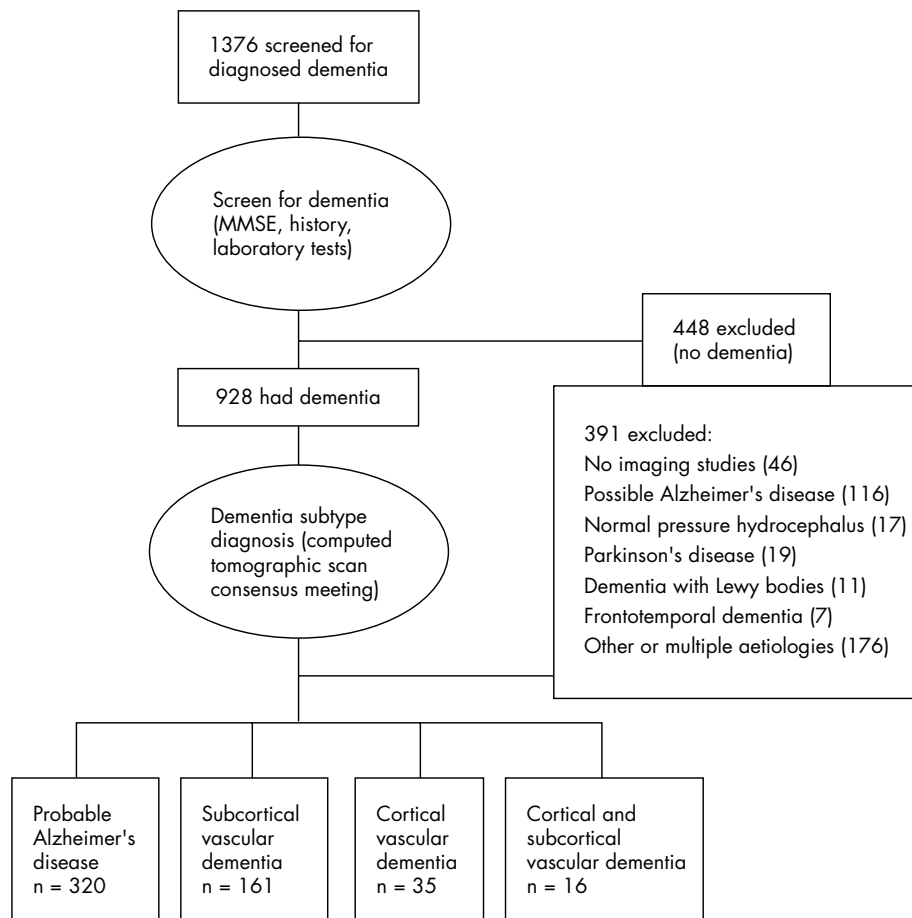


Figure 1 Flow diagram of participants meeting inclusion and exclusion criteria.

the prevalence of any NPI domain across different types of dementia. Although the prevalence of anxiety differed among different dementia types, the domain scores were not significantly different, owing to the small number of cortical VaD group.

As the prevalence of NPI disturbances might be confounded by the severity of dementia, and the cortical VaD patients had the lowest MMSE score and educational level, we conducted a linear regression analysis to compare the apathy score in each of the three groups after controlling for these two factors. The patients with cortical VaD still had higher mean scores than the patients with AD in the apathy ($\beta = 0.12$, $t = 2.75$, $p = 0.006$) and sleep disturbance ($\beta = 0.13$, $t = 2.89$, $p = 0.004$) domains. The total 12 item NPI score did not show significant differences among the different types of dementia after controlling for MMSE and educational level ($\beta = 0.10$, $t = 2.29$, $p = 0.02$)

DISCUSSION

The present study demonstrated that behavioural disturbances are very common in patients with dementia, regardless of the dementia type. Consistent with previous reports,^{23–25} our data showed only minor differences in the prevalence of behavioural disturbances in AD and VaD. It also supported past clinical reports that the differentiation of VaD from AD is difficult using clinical and neuropsychiatric features only.³ Nevertheless, specific differences in neuropsychiatric manifestations existed between patients with AD and VaD, most prominently in the domain of sleep disturbance, which was more severe in cortical VaD. Our study also revealed a trend for the severity of neuropsychiatric manifestations to be

greatest in cortical VaD and least in AD. Our study results emphasise the importance of subgrouping VaD into cortical and subcortical types.

Patients with cortical VaD had significantly higher mean composite scores in the sleep disturbance domain. This is consistent with a previous small group studies showing that VaD patients have more disrupted sleep/wake cycles and decreased sleep quality compared with AD patients.²⁶

Our study showed that patients with VaD tended to have higher scores on the apathy domain compared with AD patients, although the differences did not reach statistical significance. Apathy has been attributed to disruption of corticosubcortical circuits involving the basal ganglia, thalamus, and frontal lobes.^{27–29} AD is a cortical dementia, and the subcortical structures are largely preserved,^{30–31} whereas subcortical VaD disturbs corticosubcortical circuits with lacunar lesions and white matter ischaemic injury. Cortical lesions in VaD likewise commonly involve frontal regions and may disrupt corticosubcortical circuits mediating motivational behaviour.

Studies investigating the association of neuropsychiatric manifestations with dementia severity have failed to consistently demonstrate differences in AD compared with VaD.^{15–24 32–33} We found that some disturbances such as delusions, hallucinations, and aberrant motor activities were more common in later stages in both patients with AD and those with subcortical VaD. A large community based study found agitation and aberrant motor behaviour to be more common in participants with advanced dementia.²⁴ Our findings support this observation; we found agitation to be more common in later stages among patients with AD but

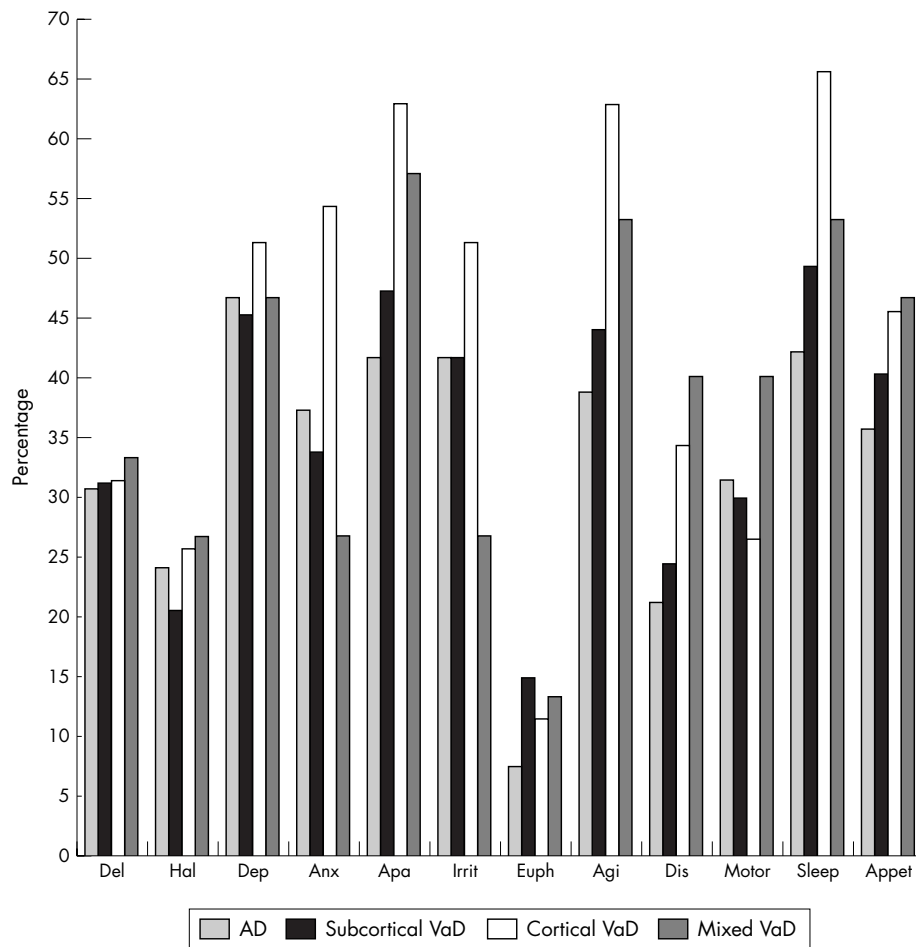


Figure 2 The prevalence of 12 Neuropsychiatric Inventory behaviours across the different types of dementia. Del, delusions; Hal, hallucinations; Dep, depression; Anx, anxiety; Apa, apathy; Irrit, irritability; Euph, euphoria; Agi, agitation; Dis, disinhibition; Motor, aberrant motor activity; Sleep, sleep disturbances; Appet, appetite changes; AD, Alzheimer’s disease; VaD, vascular dementia. *Trend of percentage differences among the different types of dementia ($p=0.03$ in the apathy domain and $p=0.04$ in the sleep disturbance domain, χ^2 test).

not VaD. The higher prevalence of neuropsychiatric manifestations in our patients may be attributable to differences in study populations (hospital based versus community based).

The strength of this study is that it was a large, prospective study using a standardised assessment tool and concomitant CT. However, there are some limitations. Firstly, because subjects who participated in this study were from a medical centre, caution should be taken in generalising the study

results. Secondly, the rate of diagnostic misclassification was uncertain because of the lack of neuropathological confirmation in our study. In this study, we attempted to identify “pure” AD and excluded subjects who fulfilled the NINCDS-ADRDA²² but also had vascular lesions on brain CT. For VaD, we used the DSM-IV criteria²¹ in addition to brain CT for diagnosis. Imaging may help compensate for the relatively low specificity of DSM-IV criteria for VaD.²¹ Mixed cases may

Table 1 Percentage frequency of Neuropsychiatric Inventory disturbances in patients with different types dementia classified by dementia severity

NPI domain	CDR = 1			CDR = 2			CDR = 3			Total		
	AD (n = 188)	sVaD (n = 82)	cVaD (n = 11)	AD (n = 107)	sVaD (n = 59)	cVaD (n = 14)	AD (n = 25)	sVaD (n = 20)	cVaD (n = 10)	AD (n = 320)	sVaD (n = 161)	cVaD (n = 35)
Delusions*†	19.9	14.1	9.1	43.9	45.9	35.7	58.3	60.9	50.0	31.0	31.1	31.4
Hallucinations*†	13.9	21.6	18.2	34.6	24.6	14.3	58.3	60.9	50.0	24.1	21.0	25.7
Depression	46.3	39.1	45.5	44.3	49.2	42.9	54.2	47.8	70.0	46.7	45.0	51.0
Anxiety	32.6	28.3	63.5	43.0	38.3	42.9	44.0	52.2	60.0	37.2	33.8	51.0
Apathy*‡	43.6	42.4	36.4	55.1	49.2	57.1	64.0	60.9	100	41.6	47.2	62.9
Irritability	38.0	42.4	36.4	45.8	36.1	50.0	50.0	60.9	70.0	42.0	41.6	51.4
Euphoria	5.3	12.0	9.1	9.3	13.1	7.1	16.0	30.4	20.0	7.5	14.9	11.0
Agitation/aggression*	28.9	39.1	45.5	49.5	47.5	71.4	64.0	52.2	70.0	38.8	44.1	62.9
Disinhibition*	13.4	18.5	9.1	32.1	26.2	35.7	32.0	45.5	60.0	21.1	24.0	34.3
Aberrant motor activity*†	17.2	18.5	18.2	49.1		23.1		40.0	31.4			
Sleep disturbance†‡	36.9	38.5	63.6	47.7	57.4	64.3	56.0	69.6	70.0	42.2	49.4	65.7
Appetite change	30.5	34.1	45.5	40.6	39.3	35.7	52.2	63.6	60.0	35.6	40.3	45.7

NPI, Neuropsychiatric Inventory, CDR, clinical dementia rating, AD, Alzheimer’s disease, sVaD, subcortical vascular dementia, cVaD, cortical vascular dementia. *Significant difference in prevalence of different CDR group among patients with Alzheimer disease ($p<0.01$, χ^2 test); †significant difference in prevalence of different CDR group among patients with subcortical vascular dementia ($p<0.01$, χ^2 test); ‡significant difference in prevalence of different CDR group among patients with cortical vascular dementia ($p<0.01$, χ^2 test).

be present in the sample despite these diagnostic procedures. Thirdly, the relatively small sample size of patients with cortical VaD might cause some differences among behavioural domains to fail to reach statistical significance. It is also possible that a few patients with very severe psychopathology had a large influence on the small number of samples and thus biased the study results.

In conclusion, the present study showed a high prevalence of neuropsychiatric symptoms in both AD and VaD. Symptoms profiles were similar in the AD, subcortical VaD, and cortical VaD groups. Sleep disturbance was most severe in the patients with cortical VaD.

ACKNOWLEDGEMENTS

This study was supported in part by grants from National Science Council (NSC-92-2314-B-075-033).

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Competing interests: none declared.

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