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ORIGINAL ARTICLE

The impact of vascular burden on behavioural and psychological symptoms in older adults with dementia: the BEVASDE study

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Abstract

Objectives Behavioural and psychological symptoms (BPS) worsen quality of life and increase institutionalization in dementia, but the relationship between BPS and vascular burden on neuroimaging is unclear. Our aim is to explore whether the profile of BPS differs between patients with large-vessel or cortical vascular dementia (cVaD), small-vessel or subcortical vascular dementia (sVaD) and Alzheimer's disease (AD).

Methods The BEVASDE study comprised 806 demented patients (cVaD—136, sVaD—184, AD—486) recruited from outpatient consultations in Salamanca and Avila, Spain. The Clinical Dementia Rating Scale (CDR) and the 12-item Neuropsychiatric Inventory (NPI) were used to evaluate dementia severity and BPS.

Results BPS were reported in 98.5%, 97.3% and 96.9% of the cVaD, sVaD and AD cases, respectively. The median NPI score was 36 in both cVaD and sVaD and 34 in AD, with a median number of four symptoms per patient. The most frequent disorders were depression (64.4%), apathy (61.8%) and sleep disturbance (60.5%). Multivariate regression analyses after controlling for possible confounders showed a higher risk of euphoria ($p = 0.011$), apathy ($p = 0.007$), irritability ($p = 0.002$) and sleep disturbance ($p = 0.020$) in cVaD than in AD and more apathy ($p = 0.0001$) and irritability ($p = 0.0001$) in sVaD than in AD. In contrast, AD subjects had a higher risk of delusions ($p = 0.007$) and hallucinations ($p = 0.023$) than patients with cVaD as well as more aberrant motor behaviour than both cVaD ($p = 0.0001$) and sVaD ($p = 0.003$).

Conclusion BPS are common in dementia and may help in differential diagnosis of the various subtypes. We should inquire about them and treat as necessary.

Keywords Behavioural and psychological symptoms · Neuropsychiatric inventory · Alzheimer disease · Vascular dementia · Large-vessel · Small-vessel

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Introduction

Behavioural and psychological symptoms (BPS) are common both in patients with vascular dementia (VaD) and in those with Alzheimer's disease (AD), affecting 80–100% of individuals at some point in the disease course [1, 2]. These disturbances have been associated with accelerated cognitive and functional decline, impaired quality of life and mortality in subjects with dementia. They also contribute significantly to increase caregiver burden, earlier institutionalization and higher costs of care [3]. However, these disorders can be treated efficiently to improve the situation when correctly diagnosed [4]. Notwithstanding the importance of these symptoms, there has traditionally been an excessive emphasis on cognitive impairment alone in the classical descriptions of most dementia subtypes, including AD.

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It is remarkable that, despite the modest body of literature dealing with BPS in VaD compared with that in AD, diagnostic criteria for VaD such as the *National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences* (NINDS–AIREN) specify that clinical features consistent with the diagnosis include personality and mood changes, abulia, depression and emotional incontinence [5]. In fact, most studies investigated a small group of VaD patients in addition to a small [6–8] or large sample of AD patients [1, 2, 4, 9–12]. Moreover, VaD is a heterogeneous entity with multiple causes [13] and only three previous reports made the differentiation between subcortical VaD (sVaD) and cortical VaD (cVaD) [14–16]. Those studies showed inconsistent results probably due to the differences in research populations, diagnostic criteria and methods to evaluate the presence of symptoms. The Neuropsychiatric Inventory (NPI) [17] was used to assess BPS in two of them [15, 16]. Fuh et al. [15] found similar neuropsychiatric profiles in patients with AD, sVaD and cVaD apart from higher apathy and sleep disturbance scores in cVaD than in AD, although the relatively small sample size of individuals with cVaD ($n = 35$) might cause some differences among behavioural domains to fail to reach statistical significance. On the contrary, Staekenborg et al. [16] demonstrated different profiles of symptoms between VaD subtypes, with especially more apathy, aberrant motor behaviour and hallucinations in sVaD and more agitation and euphoria in cVaD.

Besides the influence of different dementia subtypes on the outcome of BPS, other variables such as severity of dementia, gender, age and use of medication may be of influence as well, but these have not been taken into account in most studies [18].

The aims of the present study were to (1) compare the prevalence and severity of BPS among patients with cVaD, sVaD and AD by using the NPI scale; (2) determine how these disturbances behaved over the various stages of dementia severity; and (3) try to identify neuropsychiatric symptoms that would help differentiate dementia subtypes after controlling for demographic and clinically relevant variables.

Materials and methods

Study design, participants and setting

The *BEhavioural and psychological symptoms in VAScular DEmentia* (BEVASDE) study is a prospective study aimed to investigate risk factors and clinical and neuropsychological characteristics in patients with vascular dementia according to the vascular burden (large-vessel or cortical VaD versus small-vessel or subcortical VaD) and establish comparisons with AD and healthy populations. Subjects selected for the present research (VaD—350 and AD—500) were recruited from September 2005 to January 2007 and from February 2012 to May 2017 within the Neurology Department, Complejo Asistencial Universitario de Salamanca (CAUSA) (Salamanca, Spain) and from March 2011 to January 2012 within the Neurology Division, Complejo Asistencial de Ávila (Avila, Spain) and Outpatients Departments from which we receive referrals. The inclusion of AD patients started in September 2011.

The dementia evaluation comprised a complete medical history, physical and neurological examinations and neuropsychological testing, including the Mini-Mental State Examination (MMSE) [19]. The severity of dementia was assessed using the Clinical Dementia Rating (CDR) [20]. BPS were assessed at an interview with a responsible caregiver by using the NPI [17]. This instrument rates 12 non-cognitive symptoms; each subscale inquires whether the disturbance had been present in the last month on a four-point frequency and on a three-point severity scale. Frequency and severity scores are multiplied for each subscale (composite score; range, 0–12) and added together for the total NPI score (range, 0–144). A score of 4 or more on a subscale was used to identify the presence of a clinically relevant symptom. The scale has a high level of internal consistency reliability, inter-rater reliability and the test–retest reliability and has been validated in Spanish subjects [17, 21].

All patients underwent laboratory investigations, containing vitamin B_{12} and thyroid functions. Brain computerised tomography (CT) and/or magnetic resonance imaging (MRI) was also obtained on all participants. Patients were diagnosed as having probable AD if they met the *National Institute on Aging and Alzheimer's Association* (NIA-AA) guidelines [22]. VaD was defined according to the NINDS–AIREN criteria [5]. Subsequently, VaD patients were classified under the radiological NINDS–AIREN criteria as having cVaD (strategic large-vessel infarct of the dominant hemisphere or bilateral hemispheric strokes) or sVaD (white matter hyperintensities [WMH] involving at least a quarter of the white matter, multiple lacunes or bilateral thalamic lesions) [23].

Individuals presenting both vascular and Alzheimer features (mixed dementia), ischemic-hypoperfusive VaD, hemorrhagic VaD or other neurological disorders were excluded. Furthermore, none of the patients was affected by cancer, substance abuse, a history of head trauma with loss of consciousness, or a history of major psychiatric illness that predated the onset of dementia. Patients of each diagnosis were examined consecutively, but only those with a constant dose of antidepressants, anxiolytics, hypnotics, anticonvulsants and medication for dementia maintained for 3 months prior to evaluations were permitted, and patients who were being treated with low doses of antipsychotics and in whom discontinuation was not considered feasible were allowed to remain on their current dose. An additional selection criterion was a caregiver visiting

at least four times a week and/or living with the patient and willing to provide information necessary. After further exclusion of patients who refused to participate or did not complete the protocol, as shown in Fig. 1, 320 participants with VaD (sVaD—184, cVaD—136) and 486 participants with AD were included for data analysis (response rate, 91.4% for VaD and 97.2% for AD).

Statistical analysis

Statistical analysis was performed with SPSS 21.0 (SPSS, Inc., Chicago, IL, USA). To compare baseline characteristics between groups, χ^2 tests or Fisher's exact tests were used for categorical variables and ANOVA or non-parametric tests for continuous data. The differences in the prevalence of symptoms (present/nor present) between cVaD, sVaD and AD and between stages based on the CDR were also studied by means of the χ^2 tests or Fisher's exact tests, whereas total NPI and subscale scores were assessed by using non-parametric techniques (Kruskal-Wallis test and Brown-Forsythe test, according to the homogeneity of variances confirmed or not by the Levene test). Multiple pair-wise post hoc comparisons using standard procedures were carried out to determine those NPI domains that best differentiated each of the subgroups from the others. Subsequently, to control for age, gender, education, MMSE, dementia duration and the use of behavioural regulating medication, logistic regression analysis was conducted with the individual NPI symptoms as dependent variable and the different types of dementia (model 1, cVaD vs AD; model 2, sVaD vs AD) as independent variable. For all analyses, significance level was set at $p < 0.05$.

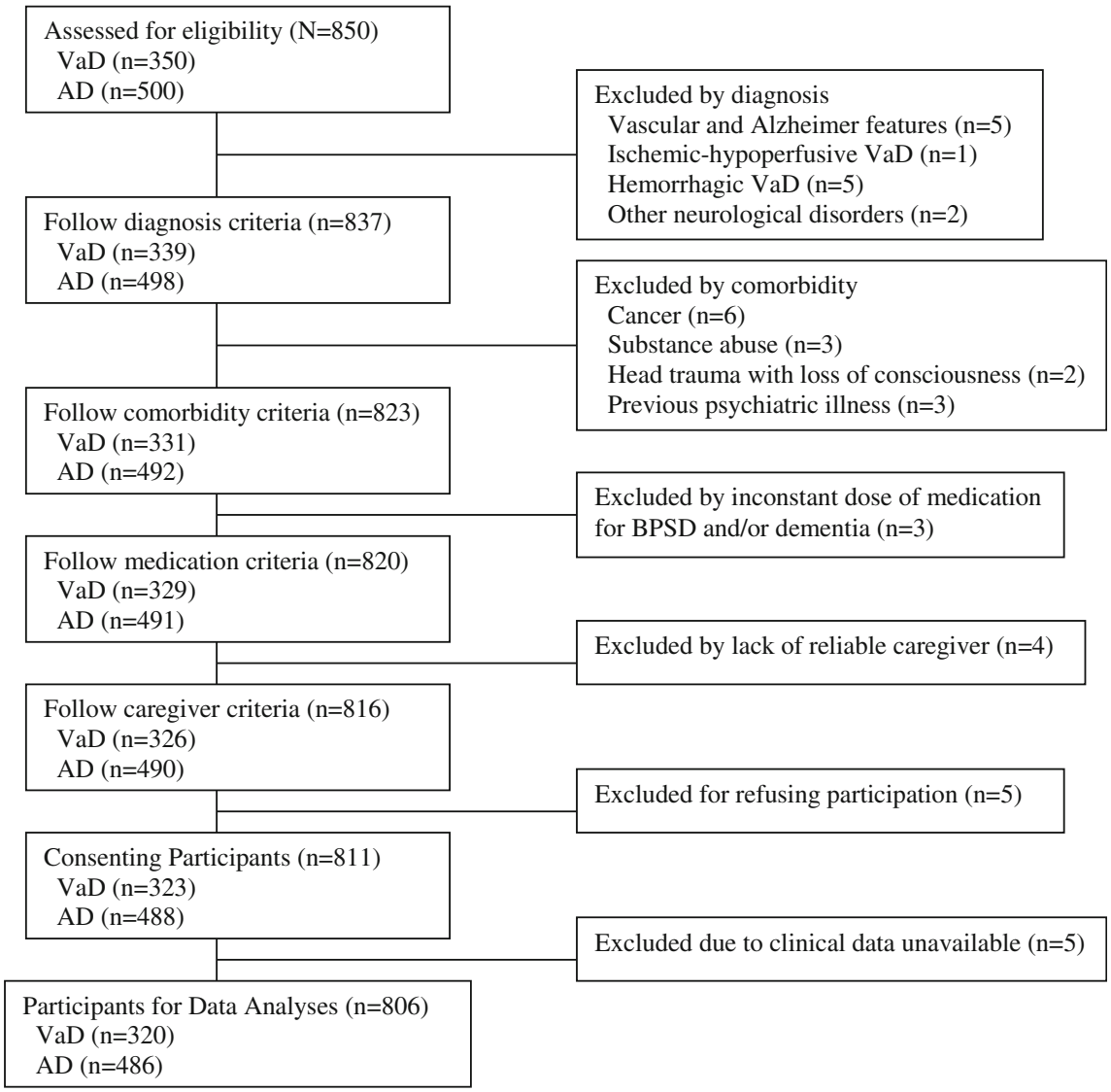

Fig. 1 Flow diagram for baseline recruitment

Results

Patients' characteristics

Demographics and characteristics of the patients in each diagnostic group are shown in Table 1. The proportion of females was significantly larger in patients with AD than in cVaD and sVaD ($p = 0.0001$). Age and education did not differ by diagnosis. The percentage of individuals from a nursing home setting was also similar among groups, albeit the duration of dementia was slightly higher in the cVaD group ($p = 0.018$). On average, patients were mildly to moderately demented. Participants with sVaD scored higher in MMSE than those with AD and cVaD ($p = 0.0001$). Similarly, the sVaD group showed the highest proportion of cases in mild stages on CDR scale, followed by the AD group ($p = 0.001$). Almost 75% of participants received any psychotropic drug (78% AD, 67% sVaD and 77% cVaD). Antidepressant consumption was higher in the AD group ($p = 0.035$), whereas subjects with cVaD and sVaD showed a significantly higher use of anticonvulsants than those with AD ($p = 0.0001$). The use of other psychotropic medications was comparable in the three groups. As expected, the participants with AD received more acetylcholinesterase inhibitors (AChEI) and memantine than those with VaD ($p = 0.0001$).

Prevalence and severity of BPS

The prevalence of NPI disturbances was similar in the three groups ($p = 0.839$). BPS were reported in 98.5%, 97.3% and 96.9% of the cVaD, sVaD and AD cases, respectively. A median number of four (0–12) symptoms per patient was reported, and in two (one sVaD and one AD) patients appeared all the 12 NPI symptoms. The most frequent disorders were depression (64.4%), apathy (61.8%) and sleep disturbance (60.5%). Disinhibition (26.9%) and euphoria (11.0%) were the symptoms that were reported most infrequently.

Figure 2 compares the prevalence of individual NPI symptoms in participants with cVaD and sVaD and those with AD. Patients with cVaD had a higher prevalence of sleep disturbances ($p = 0.002$) than patients with sVaD and AD. Participants with sVaD experienced more apathy ($p = 0.038$) than those with cVaD and AD. Subjects with cVaD and sVaD were reported as having more frequent irritability ($p = 0.0001$) compared with patients with AD. Furthermore, the prevalence of aberrant motor behaviour ($p = 0.0001$) and anxiety ($p = 0.001$) was higher in AD than in cVaD and sVaD.

The median total NPI score was 36 in both cVaD and sVaD and 34 in AD, showing cVaD subjects the highest total NPI score and those with AD the lowest total NPI score ($p = 0.038$). In addition, there appeared to be differences in the individual NPI symptoms across the three types of dementia (Table 2). Among the subdomains, both

Table 1 Patient demographics and characteristics

	AD ($n = 486$)	Cortical VaD ($n = 136$)	Subcortical VaD ($n = 184$)
Age (y), mean ± SD[a]	79.5 ± 7.1	79.8 ± 7.2	80.3 ± 6.7
Female, *n* (%)[b]	336 (69.1)	62 (45.6)	102 (55.4)**
Education (y), median (IQR)[c]	14 (9–14)	14 (10–14)	14 (10–14)
Dementia duration (y), median (IQR)[d]	3 (2.0–5.0)	4 (2.0–5.0)	3 (2.0–5.0)*
Institutionalization, *n* (%)[b]	94 (19.6)	33 (24.4)	38 (21.0)
Medication, *n* (%)			
Antipsychotics [b]	171 (35.7)	53 (39.3)	56 (30.9)
Antidepressants [b]	249 (52.0)	56 (41.5)	79 (43.6)*
Anxiolytics [b]	153 (31.9)	42 (31.1)	54 (29.8)
Hypnotics [b]	81 (16.9)	31 (23.0)	32 (17.7)
Anticonvulsants [b]	17 (3.5)	27 (20.0)	30 (16.6)**
AChEI and memantine [e]	444 (92.7)	22 (16.3)	34 (18.8)**
MMSE score, median (IQR)[d]	17 (12–21)	17 (12–21)	20 (15–23)**
CDR score, % 1/2/3[b]	40.3/38.2/21.5	31.6/47.1/21.3	50.8/38.7/10.5**
NPI, *N* (% ≥ 1)[b]	471 (96.9)	134 (98.5)	179 (97.3)
Total NPI score, median (IQR)[d]	34 (19–52)	36 (24–60)	36 (22.5–54)*

y years; *n* number; *IQR* interquartile range; *AChEI* Acetylcholinesterase inhibitors; *MMSE* Mini-Mental State Examination; *CDR* clinical dementia rating; *NPI* Neuropsychiatric Inventory

Comparison of data between Alzheimer's disease (*AD*), cortical vascular dementia (*cVaD*) and subcortical VaD (*sVaD*) was performed using [a] ANOVA, [b] χ^2 test, [c] Brown-Forsythe test, [d] Kruskal-Wallis test or [e] Fisher's exact test when appropriate. *$p < 0.05$; **$p < 0.01$

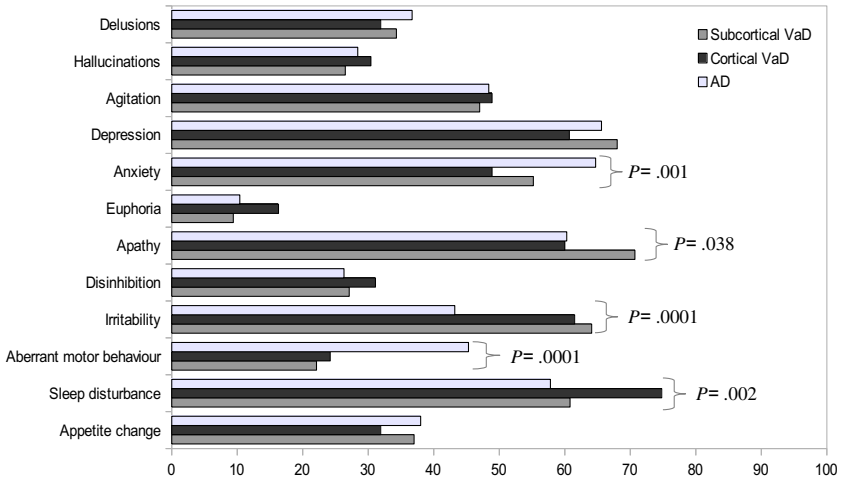

Fig. 2 Prevalence of Neuropsychiatric Inventory symptoms in Alzheimer's disease (AD), cortical vascular dementia (VaD) and subcortical VaD. Data were compared using χ^2 tests

the cVaD and sVaD groups had significantly higher mean composite scores (frequency × severity) compared with the AD group in the irritability domain ($p = 0.0001$), and there was a trend for patients with sVaD to have higher scores compared with the AD group in the apathy domain ($p = 0.009$). Moreover, cVaD subjects showed higher mean composite scores in euphoria ($p = 0.004$) and disinhibition ($p = 0.014$) than AD and in sleep disturbances ($p = 0.0001$) than both sVaD and AD. In contrast, mean aberrant motor behaviour score was significantly higher in AD compared with that in cVaD and sVaD ($p = 0.0001$).

BPS according to dementia severity

Table 3 displays the prevalence of individual NPI domain scores in patients with dementia of different severities as classified by the CDR. The prevalence of delusions, hallucinations, agitation and appetite changes increased significantly with the severity of dementia in the three groups. In AD, the differences also were statistically significant for the prevalence of euphoria, disinhibition, irritability, aberrant motor behaviour and sleep disturbance. In sVaD, the prevalence of disinhibition, aberrant motor behaviour and sleep disturbance

Table 2 Mean composite scores (frequency × severity) of individual NPI symptoms in subjects with AD, cortical VaD and subcortical VaD

NPI Domain	AD ($n = 486$)	Cortical VaD ($n = 136$)	Subcortical VaD ($n = 184$)	p value	Post hoc[a]
Delusions	2.3 (3.7)	2.4 (4.1)	2.3 (3.8)	0.990	
Hallucinations	1.7 (3.3)	2.1 (3.8)	1.6 (3.2)	0.397	
Agitation/aggression	3.0 (3.9)	3.6 (4.3)	2.9 (3.9)	0.234	
Depression	5.2 (4.7)	5.5 (5.2)	5.8 (4.9)	0.412	
Anxiety	4.5 (4.3)	4.2 (5.0)	4.0 (4.4)	0.465	
Euphoria	0.5 (1.7)	1.1 (2.9)	0.5 (1.9)	0.004	cVaD > AD
Apathy	5.3 (5.0)	5.8 (5.3)	6.6 (5.0)	0.009	sVaD > AD
Disinhibition	1.5 (3.0)	2.4 (4.2)	1.5 (3.1)	0.014	cVaD > AD
Irritability	3.2 (4.3)	6.0 (5.2)	5.4 (4.8)	0.0001	cVaD > AD
					sVaD > AD
Aberrant motor behaviour	3.7 (4.6)	1.8 (3.7)	1.7 (3.6)	0.0001	AD > cVaD
					AD > sVaD
Sleep disturbance	4.2 (4.6)	6.6 (5.0)	4.8 (4.9)	0.0001	cVaD > sVaD
					cVaD > AD
Appetite change	2.5 (3.9)	2.4 (4.1)	2.8 (4.2)	0.665	

AD Alzheimer disease; *VaD* vascular dementia; *cVaD* cortical VaD; *sVaD* subcortical VaD; *NPI* neuropsychiatric inventory

Please note that, although means (with SD) are represented in the table, statistics were performed using non-parametric tests. [a] Brown-Forsythe test with post hoc Games-Howell test

Table 3 Percentage frequency of Neuropsychiatric Inventory disturbances in patients with different types of dementia classified by dementia severity

NPI domain	CDR = 1			CDR = 2			CDR = 3		
	AD $n = 193$	cVaD $n = 43$	sVaD $n = 92$	AD $n = 183$	cVaD $n = 63$	sVaD $n = 70$	AD $n = 103$	cVaD $n = 29$	sVaD $n = 19$
Delusions*†‡	17.1	11.6	22.8	45.4	34.9	47.1	58.3	55.2	42.1
Hallucinations*†‡	8.8	11.6	10.9	32.2	33.3	44.3	58.3	51.7	36.8
Agitation/aggression*†‡	21.8	25.6	32.6	59.6	52.4	61.4	78.6	75.9	63.2
Depression†	67.4	76.7	69.6	66.7	52.4	65.7	60.2	55.2	68.4
Anxiety	66.8	46.5	58.7	65.0	46.0	57.1	60.2	58.6	31.6
Euphoria*	3.1	9.3	5.4	14.8	20.6	14.3	16.5	17.2	10.5
Apathy	54.9	55.8	67.4	66.7	63.5	75.7	59.2	58.6	68.4
Disinhibition*‡	17.6	20.9	18.5	31.7	33.3	35.7	33.0	41.4	36.8
Irritability*†	30.1	46.5	60.9	50.8	66.7	70.0	54.4	72.4	57.9
Aberrant motor behaviour*‡	26.4	25.6	12.0	56.3	20.6	30.0	61.2	31.0	42.1
Sleep disturbance*‡	43.5	65.1	52.2	63.9	77.8	67.1	73.8	82.8	78.9
Appetite change*†‡	27.5	16.3	30.4	44.8	34.9	38.6	45.6	48.3	63.2

NPI Neuropsychiatric Inventory, *CDR* clinical dementia rating, *AD* Alzheimer's disease, *sVD* subcortical vascular dementia, *cVD* cortical vascular dementia

*$p < 0.01$ among patients with AD in different CDR groups; †$p < 0.01$ among patients with cVaD in different CDR groups; ‡$p < 0.01$ among patients with sVaD in different CDR groups

was significantly higher in subjects with moderate-to-severe dementia than in those with mild dementia. In cVaD, the prevalence of depression decreased whereas irritability increased with disease progression.

Differences in BPS between Alzheimer disease, cortical and subcortical vascular dementia

Multivariate regression analyses yielded comparable results, with a higher risk of clinically relevant euphoria ($p = 0.011$), apathy ($p = 0.007$), irritability ($p = 0.002$) and sleep disturbance ($p = 0.020$) in cVaD than in AD and more apathy ($p = 0.0001$) and irritability ($p = 0.0001$) in sVaD than in AD. In contrast, cVaD subjects had a lower risk of delusions ($p = 0.007$) and hallucinations ($p = 0.023$) than patients with AD and both cVaD and sVaD participants had lower risk of aberrant motor behaviour ($p = 0.0001$ and $p = 0.003$, respectively) than those with AD (Table 4).

Discussion

The present study revealed that the occurrence of BPS was high (> 95%) in cVaD, sVaD and AD, which was consistent with previous reports [1, 2, 7, 9, 16]. Moreover, the total NPI score was found to be slightly higher in VaD. The most frequent BPS was depression, followed by anxiety, apathy and sleep disturbance in patients with AD, whereas sleep disturbance predominates in those with VaD, followed by apathy, depression and irritability. Euphoria was the least common symptom in both AD and VaD. Our results are generally in agreement with earlier reports that deal with the BPS in AD and VaD by using the NPI, although subtle differences in the rank of prevalence existed among those studies. Three previous studies also described sleep disturbance to be the commonest symptom in VaD and one of them in AD [7, 15, 24] while four reports showed apathy to be the commonest symptom in VaD and three of them in AD [2, 10, 11, 16]. Aside from the type of population (clinical, community or nursing home settings), the definition of AD/VaD and the instrument used to study the symptoms, the differences in the pattern of BPS between various studies may be due to other often unconsidered factors such as gender, age, education, use of medication and dementia severity—scarcely studied in VaD [25]. Besides, lesion volume and location may show differential effects on cognition and behaviour [26]. This is why we emphasize the importance of subgrouping VaD into cortical and subcortical types.

After controlling for potential confounders mentioned above, patients with cVaD had more euphoria and those with cVaD and especially sVaD more apathy than patients with AD. Similarly, Staekenborg et al. [16] reported agitation and euphoria to be commoner in cVaD and apathy to preponderate in sVaD. BPS such as euphoria and apathy can be observed via impairment of two different cortico-subcortical circuits, which are largely preserved in AD. Euphoria is characterized by dysfunction of the orbitofrontal circuit, in which temporolimbic structures involved in emotional and reward processing

Table 4 Logistic regression analyses of association between clinically relevant NPI symptoms (frequency × severity ≥ 4) and dementia type

Diagnosis (model)				
	Cortical VaD vs. AD		Subcortical VaD vs. AD	
NPI domain	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Delusions	*0.42 (0.22–0.79)*	*0.007***	0.88 (0.50–1.53)	0.644
Hallucinations	*0.43 (0.21–0.89)*	*0.023**	0.71 (0.37–1.37)	0.311
Agitation/aggression	0.67 (0.37–1.23)	0.195	0.88 (0.50–1.52)	0.639
Depression	1.72 (1.00–2.97)	0.050	1.46 (0.90–2.36)	0.124
Anxiety	0.70 (0.43–1.15)	0.158	0.85 (0.55–1.33)	0.491
Euphoria	*2.84 (1.28–6.33)*	*0.011**	1.71 (0.73–3.97)	0.216
Apathy	*1.94 (1.19–3.15)*	*0.007***	*2.91 (1.85–4.58)*	*0.0001**
Disinhibition	1.25 (0.72–2.18)	0.430	1.07 (0.63–1.81)	0.796
Irritability	*2.14 (1.32–3.46)*	*0.002***	*2.66 (1.71–4.14)*	*0.0001***
Aberrant motor behaviour	*0.30 (0.16–0.53)*	*0.0001***	*0.47 (0.28–0.77)*	*0.003***
Sleep disturbance	*1.84 (1.10–3.07)*	*0.020**	1.24 (0.79–1.96)	0.346
Appetite change	0.95 (0.58–1.54)	0.826	1.42 (0.92–2.19)	0.111

AD Alzheimer's disease; *VaD* vascular dementia; *NPI* neuropsychiatric inventory; *CDR* clinical dementia rating

Logistic regression analyses were adjusted for age, gender, education, MMSE, dementia duration and the use of sleep, antidepressant and behavioural medication. Values are given as odds ratio (95% CI). Statistically significant results are reported in italics. *$p < 0.05$; **$p < 0.01$

need to be integrated to properly perform complex social behaviours [27]. The association of hyperactive disturbances with hemispheric infarctions seems consistent with this interpretation. On the other hand, apathy is classically known to be frequent in subcortical ischemic vascular disease owing to the occurrence of WMH and/or lacunar infarcts in the basal ganglia and thalami, which lead to the disruption of the neural networks responsible for motivation connecting the anterior cingulated cortex (ACC), dorsomedial frontal cortex and frontal pole with the ventral aspects of the caudate nucleus, anterior and ventral globus pallidus, and dorsomedian and intralaminar thalamic nuclei [28]. In fact, one study concerning patients with CADASIL, a genetic form of VaD, suggested that patients with apathy had more severe WMH and more lacunes than patients without apathy [29]. Spalleta et al. especially highlighted the key role of the dorsal striatum in the development of pure apathy, possibly due to its function in regulating approach-attachment behaviour, affect and initiative (emotional, cognitive and motor dimensions of apathy) [30]. However, we also found cVaD patients tended to exhibit more apathy than those with AD. Our findings are supported by some previous reports with no clear association either between apathy and stroke severity or lesion volume on MRI [31].

Furthermore, sleep disturbance appeared more often in cVaD, which is in line with the idea that sleep disturbance is related to frontal lobe dysfunction. Indeed, in some studies, insomnia was associated with focal brain lesions in the left dorsomedial prefrontal area [32], and acute frontal lobe infarction was a significant predictor of insomnia [33]. Terzoudi et al. [34] found that stroke patients (without sleep-disordered breathing) had reductions in total sleep time and sleep efficiency, reduced stage II and slow-wave sleep, increased wakefulness during sleep and increased sleep latency, and this correlated with severity and outcome. The relative preservation of REM sleep in cerebellar strokes, compared with other topographies, provides evidence that REM sleep was regulated by mechanisms located in the brainstem and supratentorial hemispheric structures.

Interestingly, participants with both cVaD and sVaD were more likely to have irritability than those with AD. Lesions causing irritability are widely distributed in the brain, but most involve the structures of a neural network including the frontal lobes, limbic system, brainstem and cerebellum, or the interconnecting white matter tracts of this network. This neural network is thought to modulate the emotional motor expression [35, 36].

In contrast, we confirm that aberrant motor behaviour was more prevalent in AD than in VaD, as several earlier studies supported [1, 6, 8, 10, 11]. Aberrant motor behaviour has been found in 45.3% of our AD patients, ranging between 16 and 57% in the literature [37]. Rosen et al. [38] reported that the regions of tissue loss linked to aberrant motor behaviour included the right dorsal ACC and left premotor cortex, suggesting that aberrant motor behaviour may be a result of a failure of the reward signal to suppress activity. Instead, Rolland et al. [39] found a correlation between wandering behaviour and left parieto-temporal hypoperfusion. Notably, a recent study highlighted that asymptomatic *APOE* ε4 carriers, a recognized genetic risk factor for AD, have alterations in the connectivity

of the salience network involved in aberrant motor behaviour (right ACC and left medial frontal gyrus) without anatomic atrophy [40].

Support for a higher prevalence of delusions and hallucinations in AD patients, in comparison with cVaD, comes from recent studies showing a correlation between psychosis and hypometabolism in the right frontal/temporal and bilateral ACC [41, 42].

Finally, Frisoni et al. have suggested that a more useful way of conceptualizing BPS is as sub-syndromes, which are "clusters" of symptoms that are commonly seen together: "mood" (anxiety, apathy, dysphoria), "psychosis" (irritability, delusions, hallucinations, agitation) and "frontal" (euphoria and disinhibition), being this factor structure especially consistent in VaD and also described in AD [43, 44]. Certain authors have found four sub-syndromes: "affective" (including depression, anxiety), "apathy" (apathy, changes in appetite), "hyperactivity" (agitation, euphoria, irritability, disinhibition) and "psychosis" (hallucinations, delusions, aberrant motor behaviour and sleep disturbances), but the last two BPS may not fit so easily into any one of the sub-syndromes identified [45]. Instead, Cravello et al. reported in non-demented elderly people living in residential facilities five sub-syndromes: "affective" (depression, anxiety, night-time behaviours), "hyperactive" (agitation, irritability, appetite abnormalities), "psychotic" (delusions and hallucinations), "manic" (euphoria and disinhibition) and "apathetic" (apathy and aberrant motor behaviour) [46]. Although studying symptom groups as sub-syndromes might strengthen results and point to differences in their aetiology and treatment, the individual variability of the symptoms could not be fully explained by these sub-syndromes [47].

Strengths and limitations

Strengths of the current study include the moderate sample size of sVaD and cVaD groups in addition to the AD sample, the application of extremely high international diagnostic standards and the adjustment for multiple potential confounders (e.g. psychotropic drugs). Moreover, we use a NPI score ≥ 1 (present–not present) in order to estimate the prevalence of symptoms whereas a NPI score ≥ 4 (clinically relevant symptom) was chosen to differentiate BPS profiles, which makes our results comparable with other reports regardless of the cut-off defined. Limitations include clinical setting, subjected to referral bias that might overestimate the prevalence of neuropsychiatric symptoms; the evaluation method of BPS, which depends on caregiver information and is therefore exposed to recall bias and the cross-sectional design, since BPS can fluctuate and may not be present at every examination.

Conclusion

The present study provides evidence that cVaD, sVaD and AD show different neuropsychiatric profiles. Compared with AD, cVaD patients were more likely to display euphoria and sleep disturbance, whereas both cVaD and sVaD had a higher risk of apathy and irritability. Conversely, psychosis was experienced more frequently in AD than in cVaD. In addition, aberrant motor behaviour appeared to be more frequent and severe in the AD group than in any type of VaD. Further research should deepen on the anatomical basis of BPS for each form of dementia, being that a better knowledge on the biology of BPS could help develop more effective treatments.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The present study was performed in agreement with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The local ethics committee approved the study.

Informed consent Informed consent was obtained from all individual participants included in the study and/or their relatives and legal guardians.

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