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The Prevalence of Autonomic Symptoms in Dementia and Their Association with Physical Activity, Activities of Daily Living and Quality of Life

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Key Words
Nervous system, autonomic · Dementia · Activities of daily living · Quality of life, elderly

Abstract
Background/Aims: There is little published data regarding autonomic symptoms in dementia. This study aimed to examine the prevalence and severity of autonomic symptoms in patients with different subtypes of dementia in comparison with healthy controls, and their association with levels of physical activity, depression, quality of life and ability to carry out activities of daily living. ***Methods:*** Prevalence and severity of autonomic symptoms in Parkinson's disease dementia (PDD, n = 46), dementia with Lewy bodies (DLB, n = 32), vascular dementia (VAD, n = 38), Alzheimer's disease (AD, n = 40) and healthy controls (n = 42) were assessed using a structured symptom scale. The associations between autonomic symptoms and physical activity, Bristol Activities of Daily Living Score, Geriatric and Cornell Depression Scores and quality of life (Medical Outcomes Study 36-Item Short Form Health Survey, SF-36) were examined by multiple linear regressions. ***Results:*** Total autonomic symptom scores, urinary symptoms, constipation and postural dizziness were significantly higher in PDD, DLB and VAD patients than either controls or AD patients (all $p < 0.05$). Higher autonomic symptom scores were associated with poorer outcomes in all measures of physical activity, activities of daily living, depression and quality of life. ***Conclusion:*** The burden of autonomic symptoms is high in non-Alzheimer's dementias. The identification of such symptoms is of importance because of the detrimental effect of these symptoms upon physical activity, depression, activities of daily living and quality of life.

Introduction

There are some studies suggesting that impaired autonomic function can occur in dementia, but these studies are often small, with conflicting results [1–3]. In a previous study we did not find evidence of significant dysautonomia in Alzheimer's disease (AD) or vascular dementia (VAD) [4]. In contrast, we have found evidence of significant autonomic dysfunction in an unselected series of patients with dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) [5]. Parkinson's disease (PD), PDD and DLB are included in a spectrum of disease known as the Lewy body disorders [6]. Autonomic failure is well characterised in PD [7–9], and retrospective series of DLB cases have suggested that autonomic dysfunction is a prominent feature of DLB and PDD [10–12].

Patients with orthostatic intolerance due to generalised autonomic failure have a recognisable pattern of symptoms and aggravating factors, the most common symptoms being orthostatic dizziness, syncope and fa-

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tigue [13]. Both syncope and falls could be attributable to underlying autonomic dysfunction. Falls are a common feature of dementia, but particularly DLB [14], and they are included as supporting features in the diagnostic criteria for DLB [15]. Orthostatic dizziness and syncope have been reported as a presenting or early symptom of DLB in several case series [16, 17]. In a retrospective examination of DLB patients, urinary incontinence and constipation were the most commonly documented autonomic symptoms, occurring in 97 and 83%, respectively, whereas syncope occurred in 28% [11]. However, retrospective studies are notoriously unreliable for the detection of falls and syncope, and the detection of other autonomic symptoms relies upon the initial index of suspicion when taking the history. One prospective study has suggested that urinary incontinence occurs earlier in DLB than in AD [18].

There is little published data regarding autonomic function and autonomic symptoms in dementias other than DLB; there have been no studies comparing the prevalence of autonomic symptoms in different dementia subtypes. The use of autonomic symptom scales may be a simple, inexpensive and effective tool to aid the discrimination of DLB, AD or VAD. Another important reason for studying the prevalence and significance of these symptoms in dementia is that early diagnosis of significant autonomic failure and appropriate intervention may have the potential to reduce falls and syncope. Falls and syncope in the elderly can lead to decline in physical activity, loss of confidence, reduced ability to carry out activities of daily living and reduction in quality of life for both patients and caregivers. Finally, serious adverse outcomes such as fractures frequently lead to institutionalisation and death [19].

We aimed to examine the prevalence and severity of autonomic symptoms, the level of physical activity, depression and quality of life of patients with different subtypes of dementia in comparison with healthy controls. We hypothesised that dementia patients with a greater burden of autonomic symptoms would have reduced physical activity, increased impairment of activities of daily living and poorer quality of life.

Materials and Methods

Participant Recruitment

Patients were prospectively recruited from neurology, old age psychiatry and geriatric medical services within the Northern region of the UK. They were consecutive cases meeting one of the diagnoses AD, VAD, DLB and PDD. The diagnoses were made by operationalised criteria which have been validated against neuropathological diagnosis for DLB, AD and VAD [20, 21]. An age-matched healthy control group was recruited by local advertisement. The study received ethical approval from the Joint Ethics Committee of Newcastle and North Tyneside Health Authority, the University of Newcastle upon Tyne and the University of Northumbria at Newcastle, and the participants gave consent in accordance with the declaration of Helsinki [22].

Inclusion and Exclusion Criteria

All participants were >65 years of age. The DLB patients met consensus criteria for DLB [15]. The PDD patients met both UK Parkinson disease society brain bank criteria [23] and DLB consensus criteria, with motor disorder preceding dementia by >12 months. The AD patients met the NINCDS ADRDA criteria for AD [24], and the VAD patients met the NINDS AIREN criteria for VAD [25]. To ensure accurate application of the criteria, clinical records were subsequently reviewed and diagnostic criteria applied by 2 clinicians who were blind to the autonomic symptom, physical activity, and depression and quality of life scores of the participants. If there was disagreement between the 2 clinicians, a third person reviewed the records, and a consensus diagnosis was reached.

Participants were excluded if they were in atrial fibrillation or had other rhythm disturbance not under the control of the autonomic nervous system, or if they had a terminal illness or extreme frailty which precluded adequate participation in the study. Controls were excluded if they had any evidence of dementia or PD.

Clinical Assessment

All patients received a full medical assessment, including physical and neurological examination and 12-lead electrocardiogram. The time since diagnosis of dementia was recorded. Significant medical causes of dementia were excluded during diagnostic investigations. The severity of cognitive impairment was assessed using the cognitive subsection of the Cambridge Mental Disorders of the Elderly Examination (CAMCOG) [26].

Autonomic Symptoms

Autonomic symptoms were assessed using an autonomic symptom scale previously validated in PD patients [27]. This scale includes 12 items, each of which the participant rates as not a problem for them (scored 0), or a mild, moderate or severe problem (scored 1–3). The maximum score is 36. The items include fatigue, postural dizziness, dry eyes, nose or mouth, oily skin (seborrhoea), loss of sweating, sensitivity to glare, constipation, urinary frequency and urinary hesitancy. The 12th item in the scale, loss of libido, was replaced by dizziness on defaecation. The caregiver was asked to corroborate the history in participants with dementia.

Physical Activity

Physical activity was assessed using an activity scale previously validated in older people [28]; with scores ranging from 0 to 9, depending on the number of light, moderate or strenuous physical activities carried out during the fortnight preceding the assessment. This scale is an extension of the Nottingham Activity Scale and was used because it is able to distinguish between levels of activity at the lower end of the range of activity and is hence more relevant to older people. Examples of light activities includ-

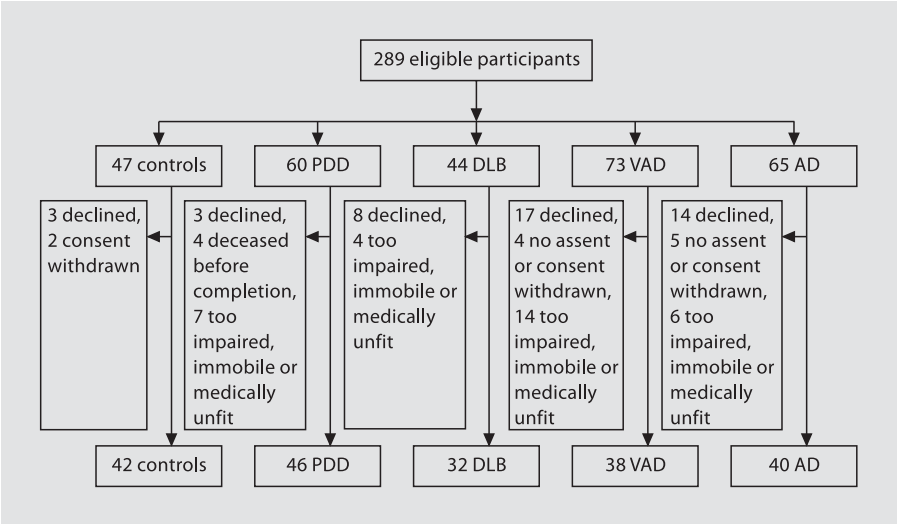

Fig. 1. Flow chart to show recruitment of patients to study.

ed leisurely walking, ironing or weeding, moderate activities were brisk walking, sweeping, gentle cycling or swimming, and strenuous activities included shovelling, hand-mowing, running or brisk cycling. The caregiver was asked to corroborate the history in participants with dementia.

Quality of Life

Quality of life was assessed using the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) [29], a generic scale which has been shown to be useful in mild to moderate dementia [30]. This scale assesses quality of life in the following domains: physical function, social function, mental health, energy/vitality, role limitation due to physical or social problems, general health and change in health.

Activities of Daily Living

Activities of daily living were assessed using the Bristol Activities of Daily Living (ADL) Scale [31]. This is a short caregiver-rated instrument consisting of 20 daily living abilities, with good face validity, construct validity and test-retest reliability, and correlates well with observed task performance.

Depression

Depression was assessed using the Geriatric Depression Scale [32] and the Cornell Scale, which has been validated for use in elderly subjects with and without dementia [33, 34].

Statistics

The presence of differences across groups in the baseline characteristics were detected using Fisher's exact test (gender) and ANOVA to compare differences across groups in normally distributed data (age, CAMCOG). Student's t test was used to compare individual groups. Kruskal-Wallis tests were used to test for differences across groups and the Mann-Whitney U test to compare differences between individual groups in non-normally distributed data (time since diagnosis of dementia, physical activity, autonomic symptom score, Bristol ADL Score and quality of life scores).

In dementia patients multiple linear regression analyses were used to examine the associations between autonomic symptom score and physical activity, Bristol ADL, depression and quality of life scores; adjusting for age, gender, diagnosis and CAMCOG score. As fatigue is a component of both the autonomic symptom scale and some of the dependent variables, analyses were repeated with fatigue partialled out. All statistical tests were performed using the SPSS version 11.0 statistics package. Significance was taken as $p < 0.05$.

Results

Baseline Characteristics

A total of 289 participants met the initial inclusion criteria, and 91 were excluded. The reasons for exclusion are given in figure 1. The remaining 198 participants were included in the study (42 controls, 46 PDD, 32 DLB, 40 AD, 38 VAD). The baseline characteristics are shown in table 1.

There were significantly more males in the VAD than in the control group ($p = 0.04$), and the VAD patients were also significantly older than the control group ($p = 0.03$) and the DLB group ($p = 0.04$). The PDD patients were significantly younger than all other groups (all $p < 0.05$). All patient groups had significantly lower CAMCOG scores than the control group (all $p < 0.05$), but the dementia groups were not significantly different from one another. The time since diagnosis of dementia was not significantly different between the dementia groups. The VAD patients had significantly more hypertension and ischaemic heart disease than all other groups (all $p <$ 0.05).

Table 1. Participant characteristics

Diagnosis	Controls (n= 42)	PDD (n = 46)	DLB (n = 32)	VAD (n = 38)	AD (n = 40)	Significant differences between individual groups
Gender, male	22 (52)	28 (61)	19 (59)	27 (71)	18 (45)	control vs. VAD: p = 0.04
Mean age ± SD	76 ± 6.7	72 ± 5.7	75 ± 7.1	79 ± 5.9	78 ± 5.6	control vs. VAD: p = 0.03 DLB vs. VAD: p = 0.04 PDD vs. all other groups: p < 0.05
Mean CAMCOG score ± SD	94 ± 4.7	64 ± 16.3	60 ± 15.0	62 ± 18.3	59 ± 14.5	control vs. all patient groups: p < 0.05
Median time since diagnosis of dementia, months	–	26 [17–50]	24 [12–45]	15 [9–28]	32 [18–45]	
Hypertension, n	11 (26)	8 (17)	7 (18)	23 (61)	4 (13)	VAD vs. all other groups: p < 0.01
Diabetes, n	3 (7)	3 (7)	2 (6)	5 (13)	3 (8)	
Ischaemic heart disease, n	9 (21)	9 (20)	6 (19)	17 (45)	7 (18)	VAD vs. other groups: p < 0.05

The figures in parentheses are percentages and the figures in square brackets inter-quartile ranges.

Autonomic Symptoms

The total autonomic symptom scores were significantly higher in the PDD, DLB and VAD patients than either controls or AD patients (all $p < 0.05$; table 2). The autonomic symptoms complained of most commonly by all participants were mucosal dryness, fatigue, urinary symptoms, constipation and postural dizziness. The prevalence of complaints of at least moderate severity of these symptoms is given in table 2. The PDD and DLB patients were more likely to complain of mucosal dryness, fatigue, urinary symptoms, constipation and postural dizziness than either the controls or AD patients. The VAD patients were more likely to complain of fatigue, urinary symptoms, constipation and postural dizziness than the controls and were also more likely to complain of urinary symptoms, constipation and postural dizziness than the AD patients. The PDD patients were more likely to complain of mucosal dryness, fatigue and urinary symptoms than the VAD patients and more likely to complain of fatigue than the DLB patients.

Physical Activity

All patient groups had significantly lower Brierley Activity Scores than the controls. The PDD, DLB and VAD patients also had significantly lower activity scores than the AD patients.

Activities of Daily Living

All patient groups had significantly worse Bristol ADL Scores than the controls ($p < 0.01$). The PDD patients also had significantly worse scores than the AD or VAD patients ($p < 0.001$), and the DLB patients had significantly worse scores than the AD patients ($p = 0.017$).

Depression

All patient groups had significantly higher depression scores, measured using the Geriatric Depression Scale, than the controls (all $p < 0.0001$). The PDD, DLB and VAD patients also had higher depression scores than the AD patients, and the PDD patients had significantly worse scores than the VAD patients. Using the Cornell Scale, the PDD, DLB and VAD patients had higher depression scores than the controls (all $p < 0.005$). The PDD and DLB patients had significantly worse scores than the AD and VAD patients ($p < 0.05$).

Association of Autonomic Symptoms with Activity, Activities of Daily Living, Depression and Quality of Life

Multiple linear regression analyses showed that a greater total autonomic symptom score was associated with poorer outcomes in all measures of physical activity, activities of daily living and depression, and in all measures of quality of life apart from role limitation due to physical problems or emotional problems. Adjusted R^2, partial ε^2 and p values are given in table 3. After the analyses were repeated with fatigue partialled out, the significant associations remained for all dependent variables except physical activity score, activities of daily living and social function. Fatigue itself was significantly associated with activities of daily living in these models, but not in the models for physical activity or social function.

Table 2. Physical activity scores, autonomic symptom scores and prevalence of individual autonomic symptoms by diagnosis

Diagnosis	Controls (n = 42)	PDD (n = 46)	DLB (n = 32)	VAD (n = 38)	AD (n = 40)	Significant differences between individual groups
Median total autonomic symptom score	2 [1–5]	9 [5–14]	7 [4–13]	5 [2–9]	3 [1–5]	controls vs. PDD, DLB, VAD: $p < 0.05$ AD vs. PDD, DLB or VAD: $p < 0.01$ PDD vs. VAD: $p < 0.05$
Mucosal dryness, n	7 (17)	19 (41)	16 (50)	11 (29)	5 (13)	controls vs. PDD, DLB: $p < 0.05$ AD vs. PDD, DLB or VAD: $p < 0.05$ PDD vs. VAD: $p = 0.03$
Fatigue, n	6 (14)	30 (65)	13 (41)	13 (34)	8 (20)	controls vs. PDD, DLB, VAD: $p < 0.05$ AD vs. PDD or DLB: $p < 0.05$ PDD vs. DLB or VAD: $p < 0.05$
Urinary symptoms, n	4 (10)	21 (46)	10 (31)	9 (24)	3 (8)	controls vs. PDD, DLB, VAD: $p < 0.05$ AD vs. PDD, DLB or VAD: $p < 0.05$ PDD vs. VAD: $p = 0.024$
Constipation, n	1 (2)	20 (43)	9 (28)	10 (26)	1 (3)	controls vs. PDD, DLB, VAD: $p < 0.05$ AD vs. PDD, DLB or VAD: $p < 0.05$
Postural dizziness, n	1(2)	14 (30)	10 (31)	6 (16)	1 (3)	controls vs. PDD, DLB, VAD: $p < 0.05$ AD vs. PDD, DLB or VAD: $p < 0.05$
Median Brierley Physical Activity Score	5 [4–8]	2 [1–3]	4 [1–4]	3 [1–4]	4 [2–4]	controls vs. all patient groups: $p < 0.01$ AD vs. PDD, DLB or VAD: $p < 0.05$
Median Bristol ADL Score	0 [0–0]	12 [9–19]	8 [4–15]	8 [7–20]	7 [4–12]	controls vs. all patient groups: $p < 0.01$ PDD vs. AD or VAD: $p < 0.001$ DLB vs. AD: $p = 0.017$
Median Geriatric Depression Score	0 [0–1]	5 [3–6]	3 [1–5]	2 [1–4]	1 [0–2]	controls vs. all patient groups: $p < 0.05$ AD vs. PDD, DLB or VAD: $p < 0.005$ PDD vs. VAD: $p < 0.05$
Median Cornell Depression Score	0 [0–1]	4 [1–8]	2 [0–5]	0 [0–3]	0 [0–1]	controls vs. PDD, DLB or VAD: $p < 0.005$ PDD or DLB vs. AD or VAD: $p < 0.05$

The figures in parentheses are percentages and the figures in square brackets inter-quartile ranges.

Discussion

To our knowledge this is the first study to investigate the prevalence of autonomic symptoms in a series of elderly patients with different subtypes of dementia in comparison with elderly controls. The associations we have shown between autonomic symptoms and reduced physical activity, activities of daily living, depression and quality of life highlight the clinical importance of such symptoms; particularly fatigue, postural dizziness, urinary symptoms and constipation.

As hypothesised, these autonomic symptoms were significantly more common in the PDD and DLB patients, both in comparison with the controls and AD patients. In addition the total burden of autonomic symptoms was higher in PDD and DLB than in the controls or AD, and the symptoms were particularly severe in PDD. Our findings are consistent with previous evidence that there is a high prevalence of autonomic symptoms in PD [7] and with previous reports of autonomic symptoms in DLB [10, 11].

The finding that the patients with AD did not complain of significantly more autonomic symptoms than the controls confirms our previous evidence that clinically significant dysautonomia is not present in AD [4]. However, we did find a higher total autonomic symptom score and prevalence of fatigue, urinary symptoms, constipation and postural dizziness in VAD. Although we

Table 3. Associations between total autonomic symptom score and physical activity, activities of daily living, depression and quality of life scores

	Adjusted R^2	Partial ε^2	p
Physical activity scale	0.118	0.059	0.005
Bristol ADL Scale	0.243	0.071	0.002
Geriatric Depression Scale	0.383	0.194	<0.0001
Cornell Depression Scale	0.191	0.044	0.017
SF-36 energy/vitality	0.447	0.173	<0.0001
SF-36 general health perception	0.411	0.146	<0.0001
SF-36 change in health	0.219	0.137	<0.0001
SF-36 mental health	0.224	0.097	0.003
SF-36 social function	0.376	0.074	0.012
SF-36 physical function	0.389	0.071	0.011
SF-36 pain	0.098	0.058	0.022
SF-36 role limitation due to emotional problems	0.177	0.041	0.065
SF-36 role limitation due to physical problems	0.332	0.034	0.089

The results of multiple linear regression analyses to examine associations between total autonomic symptom score and the outcome variables are shown, after adjustment for age, gender, diagnosis and CAMCOG score.

A higher score on the Bristol ADL Scale, Geriatric Depression Scale or Cornell Depression Scale indicates a worse outcome.

A higher score on the physical activity scale or SF-36 scales indicates a better outcome.

did not find reduced heart rate variability in VAD in our previous study, a mild to moderate degree of autonomic failure may be underlying the autonomic symptoms elicited in this study in VAD patients. In support of this we have found that dysautonomia is present after stroke in patients without dementia [35]. The extent of clinically significant autonomic failure in both VAD and stroke patients is clearly worthy of further study.

Autonomic symptoms were moderately associated with reduction in physical activity. It is not possible to infer the direction of causality of the association with physical activity from this study. Physical inactivity is known to impair autonomic function, and it is possible that the reduction in physical activity in patients with PDD, DLB and VAD is due to their concomitant impairments in mobility, with secondary reduction in autonomic function. However, neuropathological studies demonstrating the presence of Lewy bodies in the autonomic nervous system of PDD and DLB patients suggest that autonomic dysfunction is not primarily due to physical inactivity. It is possible that a combination of poor mobility and autonomic dysfunction leads to a reduction in physical activity and thus further autonomic dysfunction.

Autonomic symptoms were strongly associated with reduced activities of daily living and with depression, using scales designed for use in dementia. Dependency in activities of daily living is a predictor of nursing home placement in patients with dementia [36]. Impaired activities of daily living are also a predictor of mortality [37]. It is possible that the patient's desire to engage in both physical activity and activities of daily living is reduced by the knowledge that such activities will be accompanied by unpleasant consequences such as postural dizziness, exacerbating the decline in functional ability, which is an important feature of dementia. Alternatively, increasing autonomic symptoms and functional decline may both be a result of disease progression.

The effect of autonomic symptoms upon quality of life may be a result of the reduction in activities of daily living. Studies using generic scales and observational behavioural measures have shown that the ability to perform activities of daily living is the main factor affecting quality of life in dementia [38, 39]. Although quality of life in dementia has been shown to be stable in the majority of patients participating in longitudinal studies, a subgroup do show a significant decline, which correlates with depression, anxiety and baseline quality of life [40]. We used a generic scale to assess quality of life: the SF-36, which has reasonable reliability in mild to moderate dementia [30]. Generic scales have the advantage of simplicity and ease of use. They have clinical relevance when considering autonomic symptoms because of the expected impact of symptoms such as fatigue, postural dizziness and urinary symptoms upon general functional outcomes. Autonomic symptoms were particularly associated with poor functional outcomes, including energy/vitality, general health perception, physical function and social function. The association with such core functional outcomes emphasises the necessity of eliciting information about autonomic symptoms when evaluating patients with dementia.

The study does have some limitations. The symptom of fatigue is a core symptom of autonomic dysfunction. However, it is also an important component of depression, physical activity and quality of life. In view of this we repeated the analyses with fatigue partialled out. Fatigue contributed significantly to the degree of impairment in activities of daily living but, surprisingly, not with physical activity. Autonomic symptoms remained

associated with depression and quality of life indicators, suggesting that the effect of autonomic symptoms upon these outcomes is not entirely due to fatigue.

We used a generic scale to assess quality of life, and therefore we are not able to comment upon disease-specific quality of life outcomes. Several of the attributes of generic scales may overlap with disease-specific scales, but previous studies have shown that generic scales do not capture all of the attributes of quality of life important to patients and caregivers [41]. Patients and caregivers may also rate different attributes as important. We asked a caregiver to provide a proxy completion of the SF-36 when the patient was not able to give answers. Inevitably the patient's perception of his symptoms would have been less accurately assessed in these patients. The impact of autonomic symptoms upon disease-specific quality of life domains should be addressed in future research.

It was not possible to blind the person administering the autonomic symptom, physical activity and quality of life scales to the provisional diagnosis of the patients. However, the diagnostic criteria were also applied independently by clinicians blind to these scores. The diagnostic criteria used have been validated in a neuropathological study [21]. The autonomic symptom and physical activity scales we used have not been validated in dementia. In order to militate against this, we sought a corroborative history from the patients' caregivers. It remains possible that the prevalence of autonomic symptoms was underestimated in participants with severe dementia who were unable to give an accurate description of their symptoms.

Participants were eligible for the study only if they met one of the sets of diagnostic criteria for the dementias studied, or if they responded to local advertisement in the case of the controls. This may have resulted in the control group being generally healthier than a randomly selected sample of older people without dementia. We were not able to study the large group of older persons with mixed dementia. A truly representative study of autonomic symptoms in older people both with and without dementia would require a large epidemiological study.

In conclusion we have demonstrated that the burden of autonomic symptoms is high in non-Alzheimer's dementias, particularly DLB and PDD. The identification of such symptoms may be useful in the diagnostic assessment of dementia, but of greater importance is the effect of these symptoms upon physical activity, activities of daily living and quality of life. Future research should address whether multi-factorial interventions including physiotherapy, exercise programmes and medical management of orthostatic hypotension would improve autonomic function in these patients, resulting in a reduction of symptom burden, improved quality of life and reduced risk of adverse consequences such as falls, fractures and institutionalisation.

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