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AUTONOMIC DYSFUNCTION IN DEMENTIA

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ABSTRACT

Background:

There are no studies of autonomic function comparing Alzheimer's disease (AD), Vascular dementia (VAD), Dementia with Lewy Bodies (DLB) and Parkinson's disease dementia (PDD).

Aims:

To assess cardiovascular autonomic function in 39 AD patients, 30 VAD, 30 DLB, 40 PDD and 38 elderly controls by Ewing's battery of autonomic function tests and power spectral analysis of heart rate variability. To determine the prevalence of orthostatic hypotension and autonomic neuropathies by Ewing's classification.

Results:

There were significant differences in severity of cardiovascular autonomic dysfunction between the four types of dementia. PDD and DLB had considerable dysfunction. VAD showed limited evidence of autonomic dysfunction, and in AD, apart from orthostatic hypotension, autonomic functions were relatively unimpaired.

PDD showed consistent impairment of both parasympathetic and sympathetic function tests in comparison with controls (all $p<0{\cdot}001$), and AD (all $p<0{\cdot}03$). DLB showed impairment of parasympathetic function (all $p<0.05$) and one of the sympathetic tests in comparison with controls (orthostasis; $p=0{\cdot}02$). PDD had significantly more impairment than DLB in some autonomic parameters (Valsalva ratio–$p=0{\cdot}024$, and response to isometric exercise–$p=0{\cdot}002$). VAD patients showed impairment in two parasympathetic tests (orthostasis; $p=0.02$, Valsalva ratio $p=0.08$) and one sympathetic test (orthostasis; $p=0.04$). These results were in contrast to AD patients who only showed impairment in one sympathetic response (orthostasis; $p=0.004$).

The prevalence of orthostatic hypotension and autonomic neuropathies was higher in all dementias than in controls (all $p<0.05$).

Conclusion:

Autonomic dysfunction occurs in all common dementias but is especially prominent in PDD with important treatment implications.

INTRODUCTION

Patients with autonomic failure experience disabling postural dizziness, syncope, falls, constipation and incontinence.[1] There is a need to identify symptomatic dysautonomia in dementia in order to ensure appropriate management and reduce risk of falls, which is particularly important as falls are a significant cause of increased morbidity, institutionalisation and mortality in these individuals.[2]

There are no previous prospective studies of autonomic function comparing the most common dementia subtypes in the elderly; Alzheimer's disease (AD), Vascular dementia (VAD), Dementia with Lewy Bodies (DLB) and Parkinson's disease dementia (PDD). A generalised deficit in cholinergic function would be expected to lead to autonomic dysfunction and the common dementias have all been associated with underactivity of the cholinergic nervous systems.[3] The Braak staging of Parkinson's disease[4] emphasises early involvement of the brainstem, including the dorsal vagal nucleus, and autonomic failure is a feature of Parkinson's disease.[5]

The only previous studies using standard bedside clinical autonomic tests have mainly included patients with AD only,[6-10] although two have included patients with multi–infarct dementia or Binswanger's encephalopathy, [11,12] and there is one retrospective report of clinical autonomic dysfunction in DLB patients.[13] Studies using bedside tests do require a level of cooperation by the subject which may not be possible in dementia. These data can be enhanced by measurements of heart rate variability,[14] which requires less cooperation from the subject than other autonomic function tests and is suitable for use in patients with dementia.[15]

We examined autonomic function using a combination of standardized bedside clinical testing and heart rate variability techniques, in an unselected series of patients with a range of dementia subtypes, diagnosed according to well validated diagnostic

criteria, in comparison with appropriately matched elderly controls. Given the evidence of the retrospective study of DLB patients and evidence regarding autonomic dysfunction in Parkinson's disease (PD),[5] we hypothesised that autonomic dysfunction would be more severely impaired in DLB and PDD than in AD, and that the most severe impairment would be present in PDD due to the length of illness and severity of neurodegenerative disease.

METHODS

Participant recruitment and inclusion criteria

Consecutive patients were recruited from Neurology, Old Age Psychiatry and Geriatric Medical Services within the Northern Region of the United Kingdom. All participants were over 65 years of age. AD patients met the NINCDS ADRDA criteria for Alzheimer's disease[16] and Vascular Dementia (VAD) patients met the NINDS AIREN criteria for Vascular Dementia.[17] DLB patients met consensus criteria for Dementia with Lewy bodies.[18] Parkinson's disease with dementia patients (PDD) met both UKPDS Brain bank criteria[19] and DLB consensus criteria, with motor disorder preceding dementia by at least 12 months. 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. Participants gave consent in accordance with the declaration of Helsinki, with the involvement of caregivers and next of kin as described in detail in our previous studies in dementia.[20]

Exclusion criteria

Participants were excluded if they were in atrial fibrillation or had other arrhythmias. Controls were excluded if they had any evidence of dementia or Parkinson's disease.

Clinical Assessment

All patients received a full medical assessment, including physical examination and 12 lead electrocardiogram. Significant medical causes of dementia were excluded during diagnostic investigations. Duration of dementia, drug history and history of hypertension or diabetes mellitus were recorded. Cognitive function was assessed using the cognitive subsection of the Cambridge Examination for Mental disorders in the elderly (CAMCOG) [21]. All assessments took place in the morning; participants were asked to take their usual medications including dopaminergic agents, and to refrain from drinking caffeinated drinks or smoking on the morning on the assessment. Extra–pyramidal signs were evaluated using the motor subsection of the Unified Parkinson's disease rating scale (UPDRS),[22] after taking the usual dose of levodopa, if applicable.

Clinical Autonomic Function Tests

Clinical autonomic function tests were carried out according to Ewing's battery.[23] The electrocardiogram (ECG) was recorded during supine rest using standard limb leads I or II and locally developed software, sampling at 1 kHz. Blood pressure was monitored using a digital photoplethysmograph (Portapres, TNO, Amsterdam) which enables non invasive beat to beat blood pressure measurement. Blood pressure data were synchronised to ECG and inspected off line for artefacts, ectopic beats and non systolic waveforms which were removed using a semi–automated technique. Participants rested in the supine position for 10 minutes before starting the tests and also rested for 2 minutes between each test. Heart rate tests were excluded if invalidated by excessive ectopic activity or other arrhythmia. Blood pressure tests

were excluded if the trace was obscured by movement artefact.

Parasympathetic tests

1. Deep breathing

Respiratory sinus arrhythmia was assessed by the performance of 6 deep breaths at a frequency of 0·1 Hz. Participants were given adequate rehearsal to achieve the required frequency and counted through the 6 breaths. The response was taken as the mean of the differences between the maximum and minimum instantaneous heart rate for each cycle. A minimum of 3 breaths was required for inclusion.

2. Orthostasis

Orthostatic blood pressure and heart rate changes were assessed during a 3 minute active stand. Heart rate response to standing was assessed as the ratio of maximum R–R interval at or around the 30^{th} beat to the minimum R–R interval at or around the 15^{th} beat.

3. Valsalva ratio

The Valsalva manoeuvre was performed for 15 seconds, requiring forced expiration against an open glottis at a pressure of 40 mmHg. The pressure achieved was monitored via the PC and visual feedback was available to the participant to enable them to maintain a constant pressure. The manoeuvre was performed three times in order to maximise participant compliance and ensure reproducibility. The best response was used for analysis and a minimum of 12 seconds was required for inclusion.

Valsalva ratio was taken as the maximum R–R interval in the 15 seconds following expiration divided by the minimum R–R interval during the manoeuvre.

Sympathetic tests

1. Orthostasis

Orthostatic blood pressure change was calculated as the difference between the nadir blood pressure immediately after standing and the mean blood pressure for the 20 beats immediately prior to standing.

2. Valsalva manoeuvre

Blood pressure response was taken as the difference between the peak systolic blood pressure achieved during phase IV and the mean systolic blood pressure for the 20 beats immediately prior to the manoeuvre.

3. Isometric exercise

This was performed by rising from the supine to a sitting position, and remaining in that position for 3 minutes, without external help. The blood pressure response was taken as the difference between the mean diastolic blood pressure for the 20 beats immediately prior to sitting and the 20 beats immediately prior to the end of the sitting exercise. A minimum of 90 seconds was required for inclusion.

Measurement of Heart Rate Variability

ECG was recorded as described above. Five minutes of RR interval data were digitised and stored on computer for subsequent off–line analysis (Lab View and data acquisition card 1200, National Instruments, Newbury). Non sinus beats were removed automatically, then manually if necessary, using an R wave detection software package: the program interpolated an R wave for missed or ectopic beats.[24] The record was excluded if excessive ectopic activity or any period of supraventricular arrhythmia were present. Power spectral analysis (Fast Fourier transformation) of the edited recording was performed to obtain spectral bands in the very low (<0·04Hz), low (0·04–0·15Hz) and high (0·Б–0·40Hz) frequency bands and also total spectral power (<0·40Hz) according to international guidelines.[14] Sympathovagal balance was examined by low frequency: high frequency ratio.

Orthostatic hypotension

Sustained orthostatic hypotension was defined as a fall in systolic blood pressure of greater than 20 mm Hg or diastolic blood pressure of greater than 10 mm Hg which did not return to baseline within 30 seconds from the start of the active stand. Time of return to baseline was defined as the start of the first series of 3 consecutive beats in the blood pressure which were within one standard deviation of the baseline blood pressure.

Ewing classification of autonomic failure

Results for each bedside autonomic test were classified as normal or abnormal. A test was deemed to be abnormal if the result was below the 5^{th} percentile for that test in the control group, and borderline if below the 10^{th} percentile. Ewing's classification of autonomic function[23] was determined as shown below for each patient who had complied with sufficient tests for the classification scheme to be applied.

Normal:	all tests normal or 1 borderline
Early:	one of the 3 heart rate tests abnormal or 2 borderline
Definite:	two or more of the heart rate tests abnormal
Severe:	two or more of the heart rate tests abnormal plus one or both of the BP tests abnormal or both borderline
Atypical:	any other combination

Statistics

Fisher's Exact test was used to detect the presence of differences across groups in the categorical baseline characteristics (gender, history of hypertension, diabetes mellitus, levodopa or cardiovascular drug usage). ANOVA was used to compare differences

across groups in normally distributed data (age, CAMCOG, levodopa dose). Duration of dementia, number of cardiovascular medications and UPDRS score data were not normally distributed, therefore, Kruskal–Wallis tests were used to test for differences across groups and Mann–Whitney U test to compare differences between individual groups.

Univariate ANOVA analyses were used to establish the presence of significant differences in autonomic function tests across diagnostic groups. Heart rate variability data were transformed using the natural logarithm to produce a normal distribution. Cox regression was used to compare time of return to baseline systolic blood pressure as this was a censored event, and Fisher's Exact tests were used to compare categorical outcomes (orthostatic hypotension, Ewing classification). On the basis of our prior hypotheses, if significant differences across groups were present predefined comparisons between groups were made (univariate ANOVA or Pearson's Chi squared as appropriate). These compared each disease group with the control group, the DLB and PDD groups with the AD group and the DLB group with the PDD group. Post hoc multivariate linear regression analyses were performed to examine the potential confounding effects of age, gender, duration of dementia, hypertension, diabetes and cardiovascular medications.

All statistical tests were performed using SPSS version 11.0 statistics package. Significance was taken as $p < 0{\cdot}05$.

RESULTS

Participant characteristics

One hundred and ninety eight participants met the initial inclusion criteria (42 controls, 40 AD, 38 VAD, 32 DLB and 46 PDD). Twenty one participants were

excluded because of an arrhythmia (16 atrial fibrillation (3 controls, 1 AD, 8 VAD and 4 PDD) and 5 other arrhythmia (1 control, 2 DLB and 2 PDD)). One hundred and seventy seven participants suitable for analysis remained (38 controls, 39 AD, 30 VAD, 40 PDD and 30 DLB).

Table 1 shows the baseline characteristics of the participants. There were no differences in gender between groups (all $p>0{\cdot}05$). VAD patients were older than controls (mean difference 3·9 +/–1·6 years, $p=0{\cdot}002$), and PDD patients were younger than controls (mean difference 3·9 +/–1·4 years, $p=0{\cdot}007$). Patients with VAD had a shorter duration of dementia than those in the AD or PDD groups ($p=0{\cdot}002$, $0{\cdot}008$ respectively). All dementia groups had lower CAMCOG scores than controls (all $p<0{\cdot}001$) but the dementia groups were not different from one another.

Hypertension was more common in VAD than in all other groups and less common in DLB than in controls (VAD vs. other groups all $p<0{\cdot}01$, control vs. DLB $p=0{\cdot}017$), but there were no significant differences between groups in other factors potentially affecting autonomic function. All patient groups had higher UPDRS scores than controls (all $p< 0{\cdot}001$).

TABLE 1: PARTICIPANT CHARACTERISTICS

Diagnosis (n)	**CONTROL (38)**	**AD (39)**	**VAD (30)**	**DLB (30)**	**PDD (40)**
Gender: number of males (%) χ^2: p=0.222	18 (47)	17 (44)	21 (70)	17 (57)	23 (58)
Mean Age: years (SD) ANOVA: p<0·001	76 (7)	79 (6)	80 (6)	75 (7)	72 (5)
Median Duration of Dementia (months) (IQR) Kruskall Wallis: p=0.014	–	32 (17–48)	15 (8–28)	21 (12–44)	26 (17–51)
Mean CAMCOG score (SD) ANOVA: p<0·001	93·9 (4·7)	59·4 (14·8)	63·4 (19·0)	60·5 (15·1)	64·4 (16·8)
Hypertension: present (%) χ^2: p<0.001	15 (39)	8 (20)	22 (74)	4 (13)	10 (25)
Diabetes mellitus: present (%) χ^2: p=0.722	2 (5·2)	3 (8)	4 (13)	2 (7)	2 (5)
Number (%) receiving cardiovascular medications χ^2: p=0.532	18 (47)	26 (51)	17 (57)	16 (53)	21 (53)
Median number of cardiovascular drugs (range) Kruskall Wallis: p=0.747	0 (0–2)	1(0–3)	1 (0–3)	1 (0–2)	1(0–3)
Number (%) receiving levodopa therapy χ^2: p<0.001	0 (0)–	0 (0)–	1 (3) 150	6 (20) 225	38 (95) 447
Mean daily dose (mg)					
Median UPDRS III score (IQR) Kruskall Wallis: p<0.001	1 (0–3)	7 (3–9)	10 (7–17)	29 (14–40)	37 (30–45)

Legend to Table 1
SD: Standard deviation; IQR: Inter–quartile range; PDD: Parkinson's disease dementia; DLB: Dementia with Lewy bodies; VAD: Vascular dementia; AD: Alzheimer's disease

Clinical autonomic testing: Parasympathetic tests

Patients with PDD had impairment of all parasympathetic tests in comparison with controls in univariate ANOVA (table 2). Patients with DLB had impaired heart rate responses to deep breathing and standing in comparison with controls in univariate ANOVA (p=0·001, 0·048 respectively). All parasympathetic tests were significantly impaired in both PDD and DLB in comparison with controls in a multivariate analysis adjusting for age, gender, diabetes, hypertension and cardiovascular medications. Patients with VAD had impaired heart rate responses to standing and Valsalva manoeuvre in comparison with controls (p=0·017, p=0·008 respectively), but only the difference in Valsalva ratio remained significant in multivariate analyses (p=0·04). There were no significant differences in parasympathetic tests between AD patients and the control group.

PDD patients were more impaired in comparison with AD patients on all parasympathetic tests (all p<0·05). DLB patients had more impaired heart rate responses to deep breathing in comparison with AD patients (p=0·003). In multivariate analyses, both DLB and PDD patient groups were more impaired in comparison with AD patients on all parasympathetic tests (all p<0·05), except DLB vs. AD on response to standing (p=0.071). PDD patients had a more impaired Valsalva ratio than DLB patients (p=0·024) and this difference remained in multivariate analyses (p=0·014).

TABLE 2: PARASYMPATHETIC CLINICAL AUTONOMIC FUNCTION TESTS

Diagnosis	**CONTROL**	**AD**	**VAD**	**DLB**	**PDD**	
Mean change in heart rate during deep breathing ANOVA: p=0·002	8·15 (6·48–9·82)	7·21 (5·60–8·83) 0·42 (0.75)	6·01 (4·31–7·71) 0·07 (0.16)	4·28 (3·20–5·37) **0·001 (0.001)**	3·98 (3·08–6·29) **0·003 (0.001)**	**AD vs. DLB: 0·003 (0.01)** **AD vs. PDD: 0·03 (0.04)** DLB vs. PDD: 0·67 (0.89)
Mean heart rate response to standing ANOVA: p=0·001	1·15 (1·12–1·19)	1·13 (1·08–1·18) 0·51 (0.86)	1·09 (1·06–1·13) **0·02** (0.14)	1·10 (1·05–1·14) **0·05 (0.02)**	1·05 (1·03–1·07) **0·001 (0.001)**	AD vs. DLB: 0·25 (0.07) **AD vs. PDD: 0·002 (0.003)** DLB vs. PDD: 0·07 **(0.04)**
Mean Valsalva Ratio ANOVA: p<0·001	1·43 (1·32–1·54)	1·38 (1·29–1·47) 0·447 (0.863)	1·26 (1·19–1·33) **0·008 (0.04)**	1·28 (1·18–1·39) **0·05 (0.04)**	1·15 (1·12–1·19) **0·001 (0.001)**	AD vs. DLB: 0·16 **(0.008)** **AD vs. PDD: 0·001 (0.001)** **DLB vs. PDD: 0·02 (0.01)**

Legend to Table 2

P values in the left hand column give the result of the univariate ANOVA across all groups.

Columns 3–6: show the mean (95% confidence intervals for the mean) for each parasympathetic test by diagnosis, with p values for that patient group in comparison with the control group in univariate ANOVA, and in multivariate analyses in brackets.

The results of other predefined contrasts are given in the right hand column.

All significant results are shown in boldface.

Clinical autonomic testing: Sympathetic tests

All patient groups had a greater fall in blood pressure upon standing than controls, remaining significant in multivariate analyses (all $p<0{\cdot}05$) (table 3).

PDD patients had reduced blood pressure responses to Valsalva manoeuvre and isometric exercise in comparison with controls ($p<0{\cdot}001$), but other patient groups did not. PDD patients also had reduced blood pressure responses to Valsalva manoeuvre and isometric exercise in comparison with AD patients ($p<0{\cdot}01$), and reduced response to isometric exercise in comparison with DLB patients ($p=0{\cdot}002$). DLB patients had reduced blood pressure responses to Valsalva manoeuvre in comparison with AD patients ($p=0{\cdot}044$). None of these findings changed in multivariate analyses.

TABLE 3: SYMPATHETIC CLINICAL AUTONOMIC FUNCTION TESTS

Diagnosis (n)	CONTROL	AD	VAD	DLB	PDD	
Mean fall in systolic blood pressure on standing (mm Hg) ANOVA: p=0·01	26·6 (19·4–33·8)	45·5 (35·1–55·9) **0·004 (0.03)**	40·9 (28·2–53·5) **0·04 (0.04)**	43·2 (32·0–54·6) **0·02 (0.02)**	48·2 (39·7–56·7) **0·001 (0.005)**	AD vs. DLB: 0·75 (0.78) AD vs. PDD 0·68 (0.29) DLB vs. PDD: 0·49 (0.37)
Mean change in systolic blood pressure during phase IV of Valsalva manoeuvre (mm Hg) ANOVA: p=0·002	16·5 (9·33–23·6)	20·0 (11·1–28·9) 0·54 (0.08)	13·4 (5·59–21·2) 0·56 (0.81)	7·92 (–0·109–16·0) 0·11 (0.11)	0·792 (–3·30–4·89) **0·001 (0.001)**	**AD vs. DLB: 0·04 (0.005)** **AD vs. PDD: 0·001 (0.001)** DLB vs. PDD: 0·11 (0.12)
Mean change in diastolic blood pressure on isometric exercise (mmHg) ANOVA: p=0·001	17·2 (12·7–21·7)	15·5 (10·7–20·4) 0·611 (0.86)	12·7 (8·33–17·1) 0·15 (0.17)	15·4 (10·7–20·2) 0·59 (0.30)	4·67 (–0·22–9·56) **0·001 (0.001)**	AD vs.· DLB: 0·98 (0.80) **AD vs. PDD: 0·002 (0.002)** **DLB vs. PDD: 0·002 (0.004)**

Legend to Table 3

P values in the left hand column give the result of the univariate ANOVA across all groups

Columns 3–6: show the mean (95% confidence intervals for the mean) for each sympathetic test by diagnosis, with p values for that patient group in comparison with the control group in univariate ANOVA, and in multivariate analyses in brackets.

The results of other predefined contrasts are given in the right hand column. All significant results are shown in boldface.

Heart Rate Variability

ANOVA analyses across all groups showed significant differences in total spectral power, low frequency band and high frequency band ($p=0{\cdot}040$, $0{\cdot}041$, $0{\cdot}003$ respectively, table 4). There were no differences across groups in mean R–R interval, very low frequency band and low frequency: high frequency ratio ($p= 0{\cdot}372$, $0{\cdot}113$, $0{\cdot}428$, respectively).

Total spectral power, low frequency power and high frequency power were reduced in PDD patients in comparison with healthy controls; differences remaining in multivariate analyses (all $p< 0{\cdot}05$). Total spectral power, low frequency band and high frequency band were also reduced in comparison with the AD patient group. DLB patients were not significantly different from controls in univariate ANOVA but the low frequency band was significantly reduced in multivariate analyses ($p=0{\cdot}021$).

TABLE 4: HEART RATE VARIABILITY

Diagnosis (n)	**CONTROL (31/38)**	**AD (32/39)**	**VAD (27/30)**	**DLB (23/30)**	**PDD (38/40)**	
Total Power (ms^2)	1003 (575–1431)	820 (483–1158)	922 (332–1512)	617 (300–934)	628 (301–714)	AD vs. DLB: 0·24 (0.18)
ANOVA: p=0·04		0·49 (0.55)	0·27 (0.19)	0·08 **(0.05)**	**0·003 (0.003)**	**AD vs. PDD: 0·02 (0.02)**
						DLB vs. PDD: 0·38 (0.42)
Low Frequency Power (ms^2)	2323 (169–477)	1324 (158–490)	389 (91·5–687)	261 (85·6–438)	171 (94·0–247)	AD vs. DLB: 0·25 (0.13)
		0·41 (0.43)	0·32 (0.29)	0·059 **(0.02)**	**0·007 (0.002)**	AD vs. PDD: 0·06 **(0.03)**
ANOVA: p=0·04						DLB vs. PDD: 0·61 (0.47)
High Frequency Power (ms^2)	293 (81·3–504)	165 (99·1–232)	231 (54·4–407)	129 (46·5–212)	105 (44·0–166)	AD vs. DLB: 0·13 (0.20)
		0·89 (0.83)	0·59 (0.39)	0·10 (0.23)	**0·001 (0.01)**	**AD vs. PDD: 0·001 (0.01)**
ANOVA: p=0·003						DLB vs. PDD: 0·17 (0.25)

Legend to Table 4

P values in the left hand column give the result of the univariate ANOVA across all groups.

Columns 3–6: show the mean (95% confidence intervals for the mean) for each heart rate variability test by diagnosis, with p values for that patient group in comparison with the control group in univariate ANOVA, and in multivariate analyses in brackets.

The results of other predefined contrasts are given in the right hand column.

All significant results are shown in boldface.

Orthostatic hypotension

Sustained orthostatic hypotension was more prevalent in all four patient groups than in controls (all $p<0{\cdot}05$, table 5). Consistent with this, time for blood pressure to return to baseline after standing was significantly longer for AD, DLB and PDD in comparison with controls, remaining significant in multivariate analyses.

Ewing classification

Table 6 shows the number of cases with each Ewing classification of autonomic neuropathy by diagnostic group, and the total number of cases (%)with definite, atypical or severe autonomic neuropathy. In comparison with controls, all patient groups were more likely to have an autonomic neuropathy and severe, definite and atypical autonomic neuropathy than controls (all $p<0{\cdot}05$). PDD patients were more likely to have an autonomic neuropathy than other patient groups (AD: $p=0{\cdot}001$, VAD: $p=0{\cdot}024$, DLB: $p=0{\cdot}024$).

TABLE 5: PREVALENCE OF ORTHOSTATIC HYPOTENSION

Diagnosis	**CONTROL**	**AD**	**VAD**	**DLB**	**PDD**	
	n=38	**n=38**	**n=29**	**n=27**	**n=37**	
Number (%) of patients with sustained orthostatic hypotension Fisher's Exact test: p=0·004	5 (13)	13 (34) **0·03**	10 (34) **0·04**	14 (52) **0·001**	18 (49) **0·001**	AD vs. DLB: 0·20 AD vs. PDD: 0·16 DLB vs. PDD: 0·80
Median time (seconds) for return of systolic blood pressure to baseline (IQR) Cox regression: p=0·001	16 (12–19)	20 (12–70) **0·002**	18 (11–30) 0·06	36 (19–141) **0·001**	23 (16–73) **0·002**	AD vs. DLB: 0·29 AD vs. PDD: 0·952 DLB vs. PDD: 0·26

Legend to Table 5

P values in the left hand column give the result of the Fisher's Exact test across all groups (Cox regression in the case of time to return to baseline systolic blood pressure on standing).

Columns 3–6: show the prevalence (%) of sustained orthostatic hypotension by diagnosis, with χ^2 test for patient groups in comparison with the control group and median time to return to baseline systolic blood pressure on standing (inter–quartile range) with comparison for patient groups with the control group by Cox regression.

The results of other predefined contrasts are given in the right hand column.

All significant results are shown in boldface.

TABLE 6: CLINICAL AUTONOMIC FUNCTION TESTS (EWING CLASSIFICATION)

Diagnosis (n)	**CONTROL (34)**	**AD (31)**	**VAD (19)**	**DLB (22)**	**PDD (30)**	
Normal	29	19	9	10	5	
Early (n)	5	8	8	6	14	
Atypical (n)	0	1	1	1	4	
Definite (n)	0	1	0	5	2	
Severe (n)	0	2	1	0	5	
Atypical, definite or severe autonomic neuropathy (n (%))Fisher's Exact test: p<0·001	0 (0)	4 (13)	2 (11)	6 (27)	11 (37)	AD vs. DLB p=0·19 **AD vs. PDD p=0·03** DLB vs. PDD p=0·48

Legend to Table 6

It was not possible to classify all participants, as some were unable to complete sufficient autonomic tests to enable the Ewing classification to be calculated. Participants with dementia were less likely to have sufficient results to determine Ewing classification than were controls, but there were no differences between patient groups.

DISCUSSION

This is the first controlled study of autonomic function in AD, VAD, DLB and PDD in comparison with healthy controls. The findings, based upon a range of clinical autonomic tests and sensitive research tools, emphasise the importance of autonomic dysfunction in dementia. There were significant differences in severity of cardiovascular autonomic dysfunction between the four types of dementia. PDD and DLB had considerable dysfunction. VAD showed limited evidence of autonomic dysfunction, and in AD, apart from orthostatic hypotension, autonomic functions were relatively unimpaired. The prevalence of autonomic neuropathy as measured by the Ewing criteria was more common in all of the dementia sub types than in controls, but was especially prominent in PDD.

PDD and DLB cases both showed evidence of parasympathetic dysfunction on clinical testing, and apart from the Valsalva ratio the degree of impairment was similar. However, on sympathetic testing, PDD patients were more impaired than DLB patients, although there was some evidence of sympathetic dysfunction in DLB in multivariate analyses. Both AD and VAD patients had a higher prevalence of sustained orthostatic hypotension and autonomic neuropathy than controls, but in other group comparisons did not differ from controls.

There has been considerable debate about the diagnostic concepts of PDD and DLB. It has been suggested that in PD Lewy body pathology begins in the brainstem and progresses to the neocortex.[25] However, there may be a different pattern of evolution in DLB, with some studies suggesting that cerebrocortical pathology predominates in DLB,[26,27] although prominent Lewy body pathology is still evident in the brain stem, including the dorsal vagal nucleus.[28] In our study the profile of parasympathetic abnormalities in PDD and DLB suggest that there is

significant central autonomic involvement of the dorsal vagal nucleus in both conditions. Inevitably, the patients with PDD were taking a higher dose of levodopa, reflecting the duration of their disease. In comparisons between PDD and DLB, use of levodopa and dose are not constantly correlated, but the correlation is strong. Adjustment for levodopa use or dose in the multivariate analyses comparing PDD and DLB would therefore result in the significant differences being lost. However, this does not necessarily mean that differences between PDD and DLB were solely due to the pharmacological effect of levodopa. It is more likely that they are measuring a similar variable, namely the extent of brainstem disease, as opposed to cortical disease.

The origin of sympathetic dysfunction in Lewy body diseases has been thought to be mainly due to peripheral sympathetic denervation.[29] Cardiac ^{123}I–Meta–iodobenzylguanidine scintigraphy and neuropathological studies have found evidence of cardiac sympathetic denervation in Parkinson's disease and DLB.[30,31] Lewy body pathology can also be found in medullary regions controlling preganglionic sympathetic neurons, but with relative preservation of catecholaminergic neuronal populations.[32] Our findings suggest that sympathetic dysfunction is present in PDD and DLB, but less marked in DLB patients. This raises the possibility that there may a differential susceptibility and order of involvement of central and peripheral autonomic neurons to Lewy body pathology in DLB and PDD. This needs to be addressed in comparative neuropathological studies of the autonomic nervous system, but highlights a potentially important pathological difference between the two conditions.

The increased frequency of autonomic neuropathy in all dementias emphasises the importance of these conditions in all people with dementia. Their impact upon key

symptoms such as dizziness, syncope, falls, constipation and incontinence needs to be investigated. Specifically, the current study identifies an increased prevalence of orthostatic hypotension in all dementias. Although orthostatic blood pressure responses can be impaired for a number of reasons including medications, endothelial dysfunction and age related orthostatic hypotension, our findings remained significant after adjusting for age, gender, duration of dementia, hypertension, diabetes and cardiovascular medications, suggesting that autonomic dysfunction was possibly an attributable cause of orthostatic hypotension in these patients. No studies have compared the effects of sustained orthostatic hypotension upon the risk of falls in different types of dementia. Our findings highlight the importance of orthostatic hypotension in all patients with dementia and the need for further research into sustained orthostatic hypotension as a modifiable risk factor for falls. In elderly people without cognitive impairment, simple measures such as adequate hydration, support hosiery and pharmacological treatments such as fludrocortisone and midodrine can be used to manage orthostatic hypotension, as part of a multifactorial intervention to reduce the risk of falls.[33] Trials of multifactorial falls interventions for people with mild to moderate dementia are a priority.

Cholinergic dysfunction has been discussed as a potential cause of autonomic failure in dementia patients, and may be particularly important in PDD and DLB, where cholinergic deficits are especially pronounced, and where the disease pathology involves the dorsal vagal nucleus. In this context, it will be important to determine the impact of cholinesterase inhibitor therapy in dementia patients with autonomic impairment. Preliminary reports do suggest an adverse effect of donepezil upon autonomic function, leading to carotid sinus hypersensitivity and falls in some individuals.[34] The general impact of cholinesterase inhibitors upon autonomic

function is difficult to determine from the existing clinical trial literature, given the selected nature of the patient populations, but will be important to establish for clinical practice where patients are frailer and more likely to have autonomic symptoms.

The study included an appropriately aged control group, which is of importance because autonomic function declines with age.[35] Although the controls were slightly older than the PDD group (mean difference 3.9 +/-1.4 years), this strengthens the finding that dysautonomia is most impaired in PDD, as it is likely that even greater differences would have been found if the PDD cases were compared with younger controls. Unfortunately, the VAD group were slightly older than the control group (mean difference 3.9 +/-1.6 years), and this leads to some uncertainty with respect to the findings in this group. The abnormalities in the heart rate responses to standing and Valsalva manoeuvre may not have been present if comparisons had been made with an older control group. In addition some of the responses to the Ewing tests might not have been classified as abnormal or borderline if they were compared to a more closely age matched control group, with the result that the prevalence of autonomic neuropathy could have been overestimated. Nevertheless, the number of abnormal findings in our VAD group was few, and therefore we are able to conclude that there is not substantial dysautonomia in VAD, and that comparison with an older control group would be likely to improve the strength of this finding.

We conclude that autonomic dysfunction can occur in all common dementias in older people, but is a particularly common feature of DLB and PDD. The high prevalence of autonomic neuropathy and sustained orthostatic hypotension in dementia has potentially important implications for patient management.

Competing interests

The authors have no competing interests to declare.

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