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Orthostatic hypotension and attention in Parkinson's disease with and without dementia

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Summary To compare frequency and degree of orthostatic hypotension (OH) in Parkinson's disease (PD) and Parkinson's disease with dementia (PDD) and its effect on attention and word fluency, blood pressure (BP) and heart rate changes during tilt were determined in 10 PD and 8 PDD patients. Attention and word fluency were evaluated in supine and tilted position using standard neuropsychological tests.

OH defined as systolic BP (SBP) drop of $\geq$20 mmHg and/or diastolic BP (DBP) drop of $\geq$10 mmHg was present in 5 PDD patients and in 2 PD patients. SBP drop was significantly greater in PDD than in PD patients ($P<0.05$). Whereas word fluency was unaffected by tilt in both patient groups, attention as assessed with the Test of Everyday Attention (TEA) deteriorated significantly in the PDD group, correlating with blood pressure response (ΔSBP and TEA-2, $r=0.828$, $P<0.05$; ΔDBP and TEA-2, $r=0.828$, $P<0.05$).

We conclude that OH is frequent in PDD and should be addressed therapeutically since it may exacerbate attentional dysfunction.

Keywords: Orthostatic hypotension, attention, Parkinson's disease dementia

Introduction

Orthostatic hypotension (OH) occurs commonly in Parkinson's disease (PD) (Senard et al., 1997; Wenning et al., 1999), often exacerbated by the hypotensive effect of dopaminergic drugs (Mathias et al., 1999). Neuropathological correlates of OH in PD include Lewy Body (LB) degeneration in sympathetic ganglia (Rajput and Rozdilsky, 1976). In contrast to PD, dysautonomia including OH appears to be more common and severe in dementia with Lewy Bodies (DLB) reflecting more extensive LB pathology (Wenning et al., 1999; Thaisetthawatkul et al., 2004). Whether OH is also common in PD with delayed dementia (PDD) has not been investigated systematically, however, the widespread DLB-like neuropathology of PDD suggests that dysautonomia may be more common in this disorder compared to PD. Fluctuating attention is also frequently present in PDD patients (McKeith et al., 1996). Its underlying substrate is unclear, however, disturbances of cholinergic transmission are likely to contribute (Ballard et al., 2002). Whether impaired regulation of orthostatic blood pressure exacerbates attentional deficits in PDD has not been addressed, although several studies suggest a correlation between impaired cognitive performance and OH (Perlmuter and Greenberg, 1996; Kenny et al., 2002).

We therefore investigated the frequency and severity of OH in PD and PDD patients and assessed the impact of OH on attentional and word fluency tasks.

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Patients and methods

Patients

Two groups of patients matched for age and disease duration were included in the study.

Group 1: 10 PD patients diagnosed according to the UK Parkinson's Disease Society Brain Bank criteria (Hughes et al., 1992).
Group 2: 8 PD patients who developed dementia at least one year after the onset of parkinsonian symptoms with a Mini Mental Score <24.

The study protocol was approved by the local Ethics Committee, and informed consent was obtained from all patients or from their legal guardians.

Methods

Patients were examined in a defined off-state in the morning (Langston et al., 1992) using the Unified Parkinson's Disease Rating Scale (UPDRS I–V) (Fahn et al., 1987).

A subsequent neuropsychological interview during the on-phase gathered information on cognitive and everyday activities from caregivers, while patients received Mini Mental Status test, tests of verbal memory (verbal learning, recall and recognition), CERAD (the neuropsychological test battery developed by the Consortium to Establish a Registry for Alzheimer's Disease) (Berres et al., 2000) and executive function (Trail-Making Test A-B, NAI-FWT short version of Stroop test) (Reitan and Wolfson, 1985; Oswald and Fleischmann, 1997).

Tilt table testing was performed in a temperature-controlled room set at 22°C. BP and heart rate (HR) were continuously monitored and recorded by a Portapress device throughout the testing period of 60 min or until presyncopal symptoms suggested an imminent loss of consciousness.

After a 10 min rest period in supine position followed by 60° tilt for 10 min, patients were allowed a recovery of 10 min in supine position. During the second half of the testing period, attention and word fluency (see below) were first assessed with patients supine (10 min), followed by 10 min of recovery without testing, and during the last 10 min, the tests were re-administered with patients at 60° tilt. During each tilt-phase orthostatic symptoms were documented. The mean value of the last 30 sec of the resting period was taken as the respective baseline. OH was defined as drop of systolic BP (SBP) ≥20 mmHg and/or diastolic BP (DBP) ≥10 mmHg according to the Consensus criteria (The Consensus Committee of the American Autonomic Society the American Academy of Neurology, 1996).

Attention was evaluated with the subtest 2 and 3 of the Test of Everyday Attention (TEA-2 and TEA-3) (Robertson et al., 2006), modified by Broks et al. (1988). TEA-2 and TEA-3 evaluate attention by assessing patient counts of low pitched sounds presented in a regular sequence. To test selective attention, TEA-3 includes a distractor consisting of intermittent high pitched sounds which patients shall ignore. Patients, who had all normal hearing capacity based on clinical assessments, were asked to count low pitched sounds after an initial instruction and practice of two sequences, delivered by tapes A and B, which differ by the number of sounds to avoid learning effects. A score of 1 was given for each correctly counted sound.

Phonologic and semantic word fluency tasks were evaluated using the Regensburger verbal fluency test (Aschenbrenner et al., 2001). Patients were asked to say as many words as possible during 1 min. In the supine position, patients were asked to say words starting with P, avoiding full names or names of cities and countries (phonological fluency). Subsequently they were asked to list names of animals (semantic fluency).

During tilt, patients were asked to generate words starting with M, avoiding full names or names of cities and countries (phonological fluency). Semantic fluency was assessed asking patients to enumerate names of food.

Statistical analysis

Data were tabulated and analyzed using SPSS 12.0 for Windows (SPSS Inc., USA). The significance level was set at $P < 0.05$. Age, MMSE, disease duration, scores of word fluency and executive function are reported as mean ± standard deviation (SD), H&Y stages are reported as median (interquartile ranges).

The Student's *t*-test for normally distributed data or the Mann–Whitney-*U*-test for abnormally distributed data were used for group comparisions. Proportions of individuals in PDD and PD showing OH were estimated using Fisher's exact test. Pearson's coefficient was used to assess correlations between ΔSBP and ΔDBP and TEA-2 and TEA-3.

Results

There was no significant difference in age and disease between patient groups. PDD patients were more disabled than PD patients on their H&Y score ($P = 0.001$), and they scored significantly worse than PD patients on cognitive tests (Table 1). Co-morbidity was low in both patient groups. Hypertension was present in 2 PD patients, accompanied by diabetes mellitus type II in one patient. However, none of these patients experienced OH. Hypothyroidism in 1 PDD and 1 PD patient was well controlled.

OH was present in 5 PDD and 2 PD patients ($P = 0.088$). Orthostatic symptoms were reported by 5 PDD patients and by none of the PD patients. SPB drop was significantly greater in the PDD than in the PD group.

Table 1. *Demographic and cognitive data*

	PD	PDD	*P**
Age (years)	74.1 (±4.8)	77.3 (±7.5)	n.s.
Hoehn&Yahr	2.1 (1.8–2.4)	2.9 (2.6–3.5)	0.001
Disease duration (years)	6.4 (±4.6)	7.8 (±5.0)	n.s.
Mini Mental Status	28 (±1.4)	15 (±6.8)	<0.001
CERAD			
Verbal learning[a]	16 (±4.9)	8 (±4.4)	<0.01
Free recall[b]	6 (±2.1)	2 (±1.8)	<0.01
Recognition[c]	9 (±1.6)	4 (±2.5)	<0.01
Executive function			
Trail A	59 (±26.5)	180 (±17.5)	<0.001
Trail B	161 (±81.9)	n.a.	n.a.
NAI-FWT[d]	28 (±7.4)	121 (±59.6)	<0.01
BP/heart rate			
ΔSBP	11.8 (±27.2)	−28.3 (±36.2)	<0.05
ΔDBP	6.7 (±11.6)	−5.3 (±15.3)	n.s.
ΔHR	2.9 (±12.3)	5.1 (±6.6)	n.s.

Values are expressed as mean (±SD) or median (interquartile ranges), * group comparisons, [a] words correctly learned, [b] words correctly recalled, [c] words correctly identified from 1, *n.a.* not available, *n.s.* not significant, [d] NAI-FWT German version of Stroop Test.

Table 2. *Attention and word fluency scores*

	PD	PDD	*P**
TEA-2			
TEA-2 supine	5.6 (±1.7)	3.8 (±2.3)	0.069
TEA-2 tilt	6.3 (±1.8)	2.5 (±1.9)	0.001
ΔTEA-2	0.7 (±1.1)	−1.7 (±0.5)	<0.001
TEA-3			
TEA-3 supine	5.3 (±2.5)	3.0 (±2.1)	0.055
TEA-3 tilt	6.1 (±2.8)	1.0 (±0.9)	0.001
ΔTEA-3	0.8 (±2.1)	−1.0 (±0.9)	<0.05
Word fluency (WF)			
WF supine ("P")	6.8 (±3.2)	2.8 (±1.8)	<0.01
WF tilt ("M")	7.7 (±4.7)	4.4 (±3.3)	n.s.
WF supine ("animals")	15 (±4.7)	5.3 (±3.2)	<0.001
WF tilt ("food")	12 (±5.4)	5.6 (±2.4)	<0.01
ΔWF	0 (±3.6)	1.2 (±3.3)	n.s.

Values are expressed as mean (±SD), * group comparisons, *WF* word fluency.

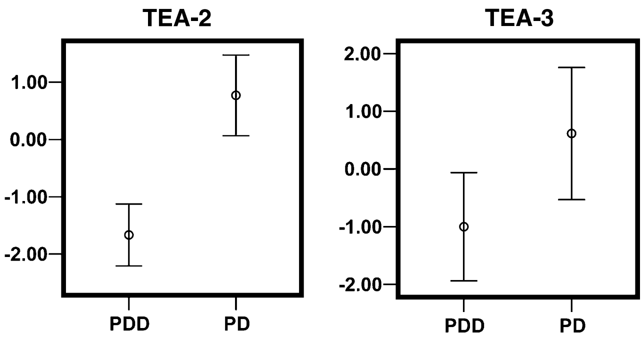

Fig. 1. Orthostatic attentional score changes between PDD and PD patients

At baseline, TEA-2 and TEA-3 scores tended to be lower in PDD than in PD patients ($P = 0.069$ and $P = 0.055$) respectively. During tilt, there was a significant decrease of TEA-2 and TEA-3 scores in PDD patients ($P < 0.001$ and $P < 0.05$), while PD patients increased both scores (Table 2, Fig. 1).

Word fluency scores were significantly reduced in the supine position in PDD compared to PD patients (Table 2). However, no significant orthostatic change of word fluency (ΔWF) was observed among PD and PDD patients.

A significant correlation between orthostatic changes in BP and attention scores was observed for PDD (ΔSBP and TEA-2, $r = 0.828$, $P < 0.05$; ΔDBP and TEA-2, $r = 0.828$, $P < 0.05$) and PD patients (ΔDBP and TEA-3, $r = 0.642$, $P < 0.05$).

Discussion

In the present study we assessed OH in PD and PDD patients in the setting of an autonomic function laboratory and evaluated the impact of OH on tests of attention and word fluency.

We observed that OH occurred more frequently in PDD than in PD patients (62.5 vs. 20%) however, this difference failed to reach significance ($P = 0.088$), and that SBP drop during tilt was significantly increased in PDD patients. Frequency of OH in our study is similar to the findings of a retrospective analysis of 20 DLB patients where OH defined as a SBP drop >30 mmHg occurred in 50% of the patients (Rajput and Rozdilsky, 1976). However, the underlying substrate of OH or BP dysregulation in PDD is unclear. In a DLB postmortem study, LB were observed in central autonomic pathways and in one single case in the intestinal Auerbach plexus (Horimoto et al., 2003). More recently, in a report of a single autopsy case, LB were also diffusely encountered in central autonomic areas as well as in ganglion cell bodies and axons (Kaufmann et al., 2004). As the pathology of DLB and PDD shows similarities, a combined involvement of central and peripheral autonomic pathways is likely to occur in PDD similar to DLB, and may thus explain the more frequent occurrence of OH in PDD patients.

In our study, PDD patients had low attentional scores which markedly decreased during tilt. The impairment of attention in PDD is believed to be related to the presence of LB in the amygdala, the hypothalamus or the insular cortex which contribute to meet behavioral demands (Critchley and Mathias, 2003) or in the anterior cingulate and orbital cortex which regulate reaction time responses (Critchley et al., 2001; Braver et al., 2001).

Nonetheless, the correlation between BP changes and selective attention tests observed in PDD patients of our study, suggests that BP changes may also contribute to attentional dysfunction in these patients. However, we cannot exclude that distraction and/or fatigue during the test procedure may have contributed to impaired attention during tilt.

On the other hand, PD patients increased BP and improved attentional scores (albeit non-significantly) during tilt, reproducing findings of a neuroimaging study examining brain activity and autonomic function during cognitive tasks, showing BP increase following cognitive tasks correlating with anterior cingulate activity in healthy subjects (Critchley et al., 2000). Moreover, a training effect may have also contributed to the improvement of attentional scores in PD patients, since cognitively intact patients are able to optimize their performance during repetitive tasks.

No influence, however, of OH on word fluency tasks was observed, indicating that attention may be more sensitive to OH than word fluency, which is probably determined by neuronal degeneration and cholinergic denervation and therefore more static.

Since OH was associated with cerebral hypoperfusion and accumulation of amyloid beta protein in cortical arterial boundary zones and other areas susceptible to ischemia in a postmortem study of 131 patients (Jendroska et al., 1995), PDD patients may be at higher risk of entering a vicious circle where the autonomic failure produces OH which favours the occurrence of degenerative lesions, aggravating the autonomic dysfunction and worsening the course of the disease.

We have demonstrated that OH occurs more frequently and more severely in PDD than in PD patients and exacerbates attentional deficits. OH may also be related to the occurrence of transient fluctuations in attention observed in PDD patients (Ballard et al., 2001), consistent with the general notion of cognitive failure resulting from chronic arterial hypotension (Mathias et al., 1999; Viramo et al., 1999).

In consequence, the maintenance of normotensive BP levels may improve cognitive functioning in PDD patients.

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