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Factors related to orthostatic hypotension in Parkinson's disease

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ABSTRACT

Introduction: Orthostatic hypotension (OH), a frequent feature of Parkinson's disease (PD) can contribute to falls and is usually related to the disease itself and/or to drugs.
Objectives: To explore factors related to OH and to assess the concordance between abnormal blood pressure (BP) fall after standing and the presence of orthostatic symptoms.
Methods: Non-demented, non-operated idiopathic PD out-patients were questioned about the presence of orthostatic symptoms. Afterward, BP was measured 5-min after lying down and for 3-min after standing up. OH was defined as systolic and/or diastolic BP fall $\geq$20 and/or 10 mmHg after standing. Patients were further evaluated by the Unified PD Rating Scale (UPDRS) and their medications were recorded.
Results: 103 patients were included in this study (mean age = 66 ± 1 years, mean disease duration = 9 ± 1 years; mean UPDRS II + III in ON-state = 37 ± 2 points). Forty-one subjects (40%) reported the presence of orthostatic symptoms during the previous week and 38 (37%) had OH according to manometric definition. Independent factors related to OH, as assessed by logistic regression were age >68 years (OR, 95% CI = 3.61, 1.31–9.95), polypharmacy (defined as intake of >5 medications, OR = 3.59, 1.33–9.69), amantadine (7.45, 1.91–29.07) or diuretics (5.48, 1.10–54.76), whereas the consumption of entacapone was protective (0.20, 0.05–0.76). The agreement between abnormal BP fall and presence of orthostatic symptoms was poor (kappa = 0.12 ± 0.1, $p = 0.23$).
Conclusion: OH was significantly related to older age, polypharmacy and amantadine or diuretics intake, while entacapone exposure appeared to reduce the risk of OH. Low concordance between OH and orthostatic symptoms was observed.

1. Introduction

Orthostatic hypotension (OH) affects 20–65% of patients with Parkinson's Disease (PD), depending on the type of patients and the working definition of OH [1,2]. Symptoms include generalized weakness, lightheadedness, vertigo or syncope in the worst cases [3]. OH can cause falls and increase the risk for cognitive dysfunction [4]. In the elderly, OH has been also shown to predict all-cause mortality [5]. These data emphasizes the importance of its prompt recognition and treatment. Interestingly, in some cases, OH can precede PD diagnosis, highlighting its importance as a preclinical marker [1].

Altered cardiovascular reflexes are the hallmark of OH in PD [6]. Abnormal blood pressure responses to the Valsalva maneuver and markedly decreased baroreflex gain, among others, are usually observed in PD. These alterations probably result from cardiac sympathetic denervation, which has been demonstrated in PD by neuroimaging techniques and/or from impaired vasoconstriction due to vascular sympathetic denervation, according to the so-called double hit hypothesis [6]. Finally, basal ganglia alterations can be also responsible for cardiovascular autonomic system dysfunctioning [7].

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Drugs are also known to induce or aggravate OH. For example, levodopa or dopamine agonists administration can cause or worsen OH [8]. Other drugs such as antihypertensives, diuretics, antidepressants or antipsychotics are also common causes of OH [9]. Thus, this study was set out to further characterize the effects of demographical characteristics, PD duration and severity as well as of dopaminergic or non-dopaminergic drugs on OH occurrence in PD. Additionally, the concordance between abnormal BP fall after standing and the presence of orthostatic symptoms was explored.

2. Methods

2.1. Sample

Consecutive PD patients were recruited from 2 tertiary Movements Disorders Centers at the Neurological Departments of Toulouse and Bordeaux University Hospitals (France). Patients were included if they fulfilled the UKPDSBB criteria for idiopathic PD. Patients with previous neurosurgical interventions for PD or with cognitive impairment preventing collecting data in a reliable manner were excluded.

This study was approved by the local ethical committee. Informed consent was obtained before participation of all patients.

2.2. Procedures

PD patients were approached while attending the out-patient clinic for a regular medical consultation. Parkinsonian symptoms were evaluated by means of the Unified Parkinson's Disease Rating Scale (UPDRS) parts I–IV. Patients were then asked by the same investigators (SPLL or MVR) if they have had any of the following symptoms during the precedent 7 days: dizziness, vertigo, lightheadedness, postural instability, fainting or falls after standing up [2]. Afterward, subjects lied down in a quiet room for 5 min, after which blood pressure (BP) was measured by a calibrated sphygmomanometer. Subjects were then asked to stand up and BP was measured every min for the first at 3 min. OH was defined by consensus as a drop in systolic and/or diastolic BP (SBP or DBP) $\geq$20 or 10 mmHg within 3 min after standing up [10].

All patients were assessed in the morning and had received their medications as on a normal day. All medications taken by the patients were recorded and codified according to the World Health Organization Anatomical Therapeutic Chemical classification system (WHO-ATC). Polypharmacy was defined as intake of >5 medications [11].

2.3. Statistical analysis

A sample size calculation found that 100 subjects would allow for the detection of odds ratio $\geq$2.5 when analyzing factors related to OH. This sample size would also be enough to detect a difference of 0.2 points in kappa agreement coefficient assuming a no-agreement null hypothesis (i.e. $k = 0$).

Unpaired Student *t*-test or Chi-square test was employed for bivariate comparisons of numerical or categorical variables. Forward logistic regression was used to disclose independent factors related to OH. Only correlates with a significance level in the bivariate analyzes were included in the models as explanatory variables. Model's goodness of fit was explored by the Hosmer & Lemeshow score. Potential interactions and multicollinearity were explored and were absent. Numerical independent variables were dichotomized to their median values to facilitate results interpretation.

Kappa coefficient was calculated for assessing the agreement between the presence of orthostatic symptoms and the presence of OH. Kappa coefficients were considered: $\leq$0 = poor, 0.01–0.20 = slight, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = substantial, and 0.81–1 = almost perfect.

Analyzes were performed by SPSS v18 (SPSS Inc, Chicago Ill).

3. Results

One hundred ten subjects were approached for the study, all of whom agreed to participate. Seven subjects had to be excluded due to missing data. The demographics of the final 103 evaluated patients are shown in Table 1. Thirty-eight out of the 103 studied patients fulfilled the manometric criteria for OH (37%). The relationship between OH and several variables is presented in Table 2. Bivariate analyses showed that subjects with OH were older, had more severe PD, were more frequently on >5 medicines, were more frequently on amantadine or diuretics and less frequently on entacapone (Table 2). A forward logistic regression model showed that age >68 years (odds ratio, 95% confidence interval: 3.61, 1.31–9.95), polypharmacy (3.59, 1.33–9.69), exposure to entacapone (0.20, 0.05–0.76), amantadine (7.45, 1.91–29.07) or diuretics (5.48, 1.01–54.76) was the only significant independent predictors. Fig. 1 shows the effects on the risk of OH of the number of medications taken by the patients, the interaction between levodopa and entacapone as was well as amantadine effect (panels A–C respectively). As shown in panel A, taking more than 5 drugs was significantly related to the presence of OH, while taking between 2 and 5 drugs was almost significantly related. When levodopa was

Table 1
Sample characteristics.

Age (years)	66.5 ± 0.9
PD duration (years)	9.4 ± 0.6
Males	73 (72%)
UPDRS II + III score	36.6 ± 1.7
Hoehn &Yahr score	
I/I.5	6 (5%)
II/II.5	76 (75%)
III/IV	20 (19%)
Dyskinesias	47 (46%)
Wearing-off	43 (42%)
Dopaminergic therapy	
No	1 (1%)
DAs	11 (11%)
LD	19 (18%)
DAs + LD	72 (70%)
MAO-B Inhibitors	9 (9%)
Entacapone	26 (25%)
Amantadine	16 (16%)
Orthostatic hypotension	38 (37%)
Hypotensive symptoms	41 (40%)

Shown are means ± standard error of the mean for numerical or *n* (%) for categorical variables. DAs = Dopamine agonists, LD = levodopa. MAO-B = Monoamine oxidase B.

Table 2
Factors related to orthostatic hypotension (OH).

	No OH ($n = 65$)	OH ($n = 38$)	Bivariate *p*-value	Multivariated OR (95% CI)
Male gender	44 (69%)	29 (78%)	0.30	
Age > 68 years	27 (42%)	26 (68%)	0.008	3.61 (1.31–9.95)
UPDRS I > 3	19 (30%)	16 (42%)	0.20	
UPDRS II + III > 33	26 (41%)	25 (66%)	0.01	2.21 (0.81–6.07)
PD duration > 9 years	28 (43%)	20 (53%)	0.34	0.82 (0.21–1.90)
Dyskinesias	29 (45%)	18 (47%)	0.80	
Fluctuations	30 (46%)	13 (34%)	0.25	
Polypharmacy*	17 (26%)	21 (55%)	0.03	3.59 (1.33–9.69)
Exposure to >3 antiparkinsonians	26 (40%)	16 (42%)	0.80	
Drugs				
Levodopa	57 (88%)	34 (89%)	0.78	
Dopamine agonists	54 (83%)	29 (76%)	0.40	0.79 (0.23–2.75)
MAO-B inhibitors	5 (8%)	4 (11%)	0.62	
Entacapone	21 (32%)	5 (13%)	0.03	0.20 (0.05–0.76)
LDED > 1050 mg/day	31 (48%)	19 (50%)	0.80	
Amantadine	5 (8%)	11 (29%)	0.004	7.45 (1.91–29.07)
Imipraminic antidepressants	1 (2%)	1 (3%)	0.70	
Selective serotonin reuptake inhibitors	6 (9%)	5 (13%)	0.50	
Exposure to >2 antihypertensives	6 (9%)	5 (13%)	0.40	
Diuretics	0 (0%)	3 (8%)	0.02	5.48 (1.01–54.76)
Beta-blockers	6 (9%)	7 (19%)	0.20	
Calcium-channel antagonists	7 (11%)	3 (8%)	0.64	
Renin-Angiotensine blockers	11 (17%)	3 (8%)	0.19	

OR = Odds ratio; MAO-B = monoamino-oxidase B; *Polypharmacy = intake of $\geq$5 medicines.

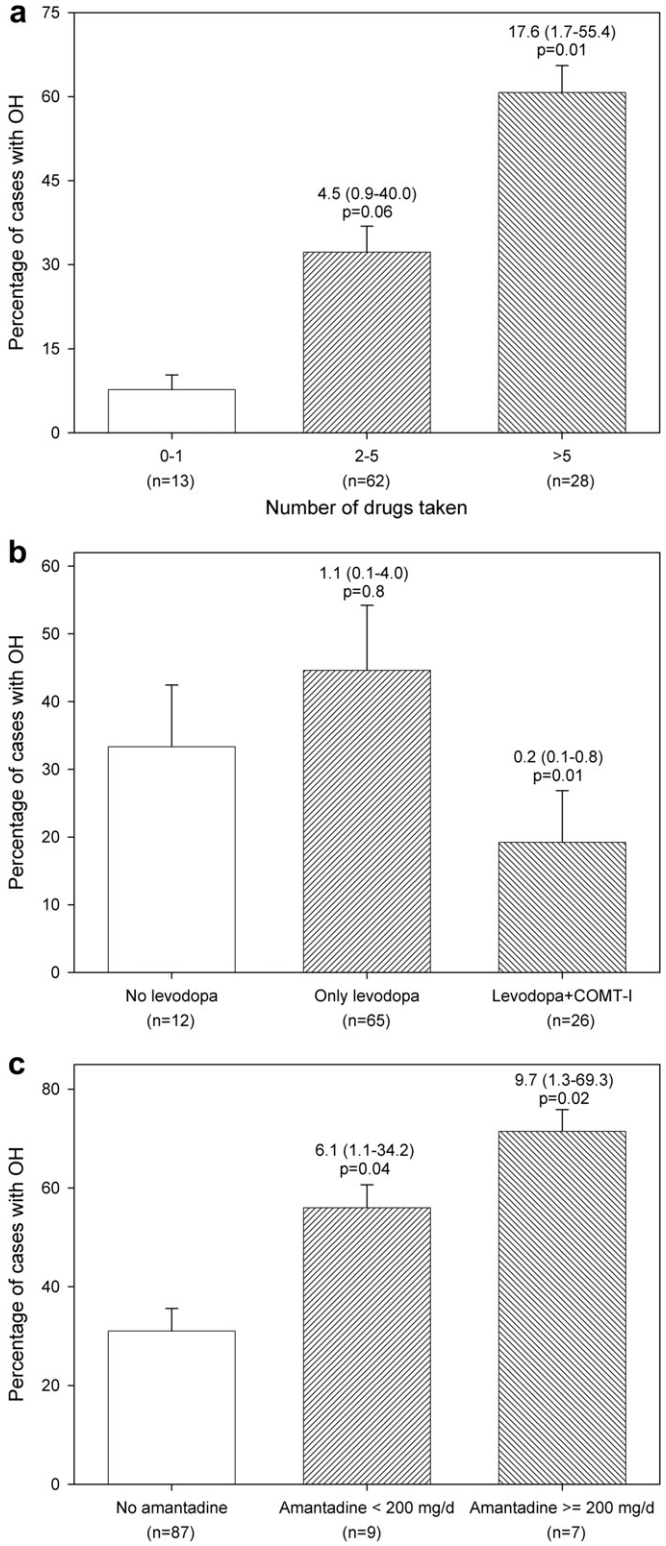

Fig. 1. Effects of number of medications (a), entacapone–levodopa interaction (b) or amantadine dose on orthostatic hypotension (OH) risk. Odds ratio (95% confidence interval) and *p*-values shown were taken from the logistic regression model and are thus adjusted for age and diuretics intake.

given alone, OH was more frequent, but the difference was not significant taking subjects not on levodopa as the reference group (panel B). On the other hand, exposure to entacapone significantly reduced the risk of OH (panel B). Exposure to amantadine at doses lower than 200 mg/d increased the risk of OH by six-fold, while higher doses increased it further by a factor of 9 (panel C).

The concordance between the presence of manometric OH and the presence of orthostatic symptoms was poor and non-significant (kappa $= 0.12 \pm 0.10$, $p = 0.23$, Table 3). When SBP and DBP fall after standing were considered separately, only the former showed significant correlation with orthostatic symptoms (0.19 ± 0.09, $p = 0.04$), which was nonetheless still considered slight (Table 3).

4. Discussion

Factors related to OH have been insufficiently studied in PD so far. Most studies dealing with this topic did not try to discriminate the influence of disease severity or duration and the pharmacological treatments using multivariate statistical methods [2,4,12,13], while this approach has become the standard procedure in epidemiological studies [14]. Moreover, no study has considered the effect of OH-inducing drugs. Conversely, in our study, potential OH-inducing drugs were identified according to the literature and data were analyzed by multivariate methods. Besides the well known association between age and OH, we could reveal some previously unidentified factors connected to OH in PD. Most notably, polypharmacy as well as exposure to diuretics or amantadine were associated with increased OH frequency, while entacapone appeared to display protective effects.

OH was evaluated in this study following the most recent international consensus [10]. These procedures allowed to identify that 37% of PD subjects with a mean age of 66 years and moderate PD (UPDRS II + III = 36) attending 2 different specialized movement disorders out-patient clinics exhibited an abnormal BP fall within the first 3 min after standing. This is in line with previous reports [1,2]. The presence of OH beyond 3 min was not explored. Patients with BP drop beyond this point may represent mild or early forms of sympathetic failure and its clinical significance remains unclear [10]. Further studies are needed to check if these results can be extended to other types of patients.

The correlation between manometric OH and orthostatic symptoms was weak (i.e. kappa ≤ 0.2) and in general few patients presented both conditions. These results agree with previous evidence showing a poor concordance of orthostatic symptoms with BP fall, even when using tilt test for evaluations [15]. It has been suggested that optimal OH evaluation should capture an extended time span, for example by utilizing 24-h ambulatory blood pressure monitoring [16].

One hundred patients were included in our study according to a power analysis. Nonetheless, exposure to some drugs, such as entacapone or diuretics was rather infrequent (i.e. <10 patients in some groups), thus somewhat limiting the validity of our results. Therefore, these results should be confirmed in larger samples.

Our observation of a close relationship between age and OH is consistent with previous studies in non-PD subjects showing that in 4931 community-dwelling, non-institutionalized persons aged 65 years and older, OH prevalence increased from 15% in the 65–69 years group to 26% in those older than 85 years in a linear fashion [17]. Cumulating evidence indicates that age is also an important determinant in PD [4,13]. Some studies have also suggested that OH is related to PD severity [2,12]. In our study, the strength of the association between these factors was high (i.e. OR > 2), but it was not statistically significant, thereby suggesting insufficient power.

Among the modifiable risk factors analyzed, drug consumption appeared as a major determinant of OH. Not only particular drugs, such as diuretics or amantadine were independently correlated to the presence of OH, but also to the total number of consumed medications. These factors have not been studied in PD previously, to the best of our knowledge. Conversely, in the general population,

Table 3
Blood pressure response to standing according to the presence of orthostatic symptoms.

		No orthostatic symptoms ($n = 62$)	Orthostatic symptoms ($n = 41$)	Kappa score	p-value
SBP and/or DBP fall ≥20/10 mmHg	No	42 (68)	23 (56)	0.12 ± 0.10	0.23
	Yes	20 (32)	18 (44)		
SBP fall ≥20 mmHg	No	49 (79)	25 (61)	0.19 ± 0.09	0.04
	Yes	13 (21)	16 (39)		
DBP fall ≥10 mmHg	No	50 (81)	30 (73)	0.09 ± 0.09	0.37
	Yes	12 (19)	11 (27)		

Standard errors of the mean for kappa scores are shown.

polypharmacy have been shown to increase the risk of OH. Poon and colleagues found that the prevalence of OH in 505 patients attending a geriatric clinic increased from 35% to 58%, 60% and 65% in those who received 0, 1, 2 or ≥3 potentially causative medications (i.e. antihypertensives, diuretics, alpha-blockers, antidepressants or antipsychotics) respectively [9]. Our study shows essentially similar results, as the number of drugs was almost linearly correlated to the risk of OH (Fig. 1a). It is possible that polypharmacy may have acted as an indicator of sicker patients, but other explanation such as presence of drug interactions cannot be ruled out.

Using the British Women's Heart and Health Study database it was found that exposure to ≥3 antihypertensive drugs was a significant predictor of OH in older women [18]. Our study also showed that diuretic exposure was significantly related to OH in PD.

Several studies have suggested that OH is more frequent in patients on levodopa or dopamine agonists [2,4,13]. We found a greater proportion of OH among levodopa-consumers versus patients not on levodopa, but this did not reach statistical significance (Fig. 1c). Nonetheless, this result is biased by the absence of a true reference group, as subjects not receiving levodopa may have been exposed to other antiparkinsonian drugs, such as dopamine agonists or MAO-B inhibitors. Interestingly, in our study, dopamine agonists were not related to OH in the multivariate analysis. In fact, we found that OH was less frequent in patients treated with dopamine agonists. This may indicate a bias, as patients on dopamine agonists could have been younger and thus less prone to suffer from OH. It may also be possible that physicians may have chosen to avoid treating patients at high risk of OH with dopamine agonists. This illustrates an important limitation of our study, which is that correlation measures associations between pairs of variables, but not causation. Therefore our results should be interpreted with caution.

We observed that patients on levodopa + entacapone had a reduced risk of OH. To other knowledge there are no previous reports about a potential antihypotensive effect of entacapone. Such effect is surprising since entacapone increases the bioavailability of levodopa and is then commonly considered at risk of increasing the risk of dopaminergic adverse drug reactions, including OH [19].

The cardiovascular effects of entacapone were assessed in 15 PD patients after a 1-week treatment with entacapone 200 mg with each levodopa dose [20]. Results failed to show any effect, which might be explained by insufficient power or exposure length. Furthermore, in agreement with our observations, the frequency of OH was also found to be lower in subjects on levodopa + carbidopa + entacapone as compared to those on levodopa + carbidopa in one 12-month double-blind, placebo-controlled study, although the difference did not reach statistical significance [21]. Moreover, Catechol-O-methyl transferase enzyme inhibition has been shown to block peripheral norepinephrine (NE) degradation [22], contributing thus to an increased synaptical NE content. Accordingly, tolcapone has also been reported to increase circulating NE levels [23]. In view of the herein reported results, the putative effects of entacapone on cardiovascular functioning should be revisited.

As suggested by the *Summary of Product Characteristics* [24], amantadine was connected to OH in our sample. The mechanism for such an effect, as for the other pharmacodynamic effects of this old "dirty" drug, remains unclear. Amantadine is supposed to enhance dopamine release, and this might account for a dopaminergic mechanism for OH. In France, amantadine is mainly used in severely advanced PD patients who suffer from dyskinesia. However, the correlation between OH and the consumption of amantadine remained in the multivariate analysis after adjusting for disease duration and severity. Other explanations should then be looked for. Amantadine has arrhythmogenic properties which has been shown to be important in case of overdoses [25]. Animal models found that low doses of amantadine may have a negative inotropic and chronotropic activity by blocking Ca^{++} influx [26]. At higher doses it can also block cardiac muscarinic receptors [27]. Additionally, activation of NMDA receptors in the nucleus tractus solitarii, through increase in levels of nitric oxide and L-glutamate, is involved in the bradycardic responses to chemoreflex activation [28]. In humans, OH was reported as a side effect of amantadine in one child during an open-label trial with this drug [29]. Finally, memantine, an aminoadamantane derivate chemically related to amantadine, has been recently found to cause bradycardia, OH with falls, fainting or malaise with arterial hypotension [30]. In our study, only 16 subjects were on amantadine, but a dose-response relationship could be shown (Fig. 1b). Therefore, our results further suggest that amantadine treatment may play a role per se in the genesis of OH and that its use might be reconsidered in PD patients with OH.

In summary, age, polypharmacy and exposure to amantadine or diuretics were the main factors related to OH after multivariate analyses including most of the known factors related to OH. While age is a non-modifiable risk factor, OH should be closely monitored in PD patients on polypharmacy, diuretics or amantadine. Entacapone exposure was found to reduce OH risk.

Conflict of interests

SPLL, MVR, NF, US and JLM disclose no conflict of interests. FO has received scientific grants from Novartis and Abott. OR has act as an advisor for most drug companies developing antiparkinsonian medications and has received unrestricted scientific grants from GSK, Novartis, Boehringer-Ingelheim, Faust Pharmaceuticals, Eisai, Lundbeck, TEVA, Euthérapie, Solvay.

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