Non-dipping nocturnal blood pressure and psychosis parameters in Parkinson`s Disease

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Background: Non-motor symptoms are increasingly recognized in Parkinson's Disease (PD) and include physical as well as psychological symptoms. A psychological condition that has been well studied in PD is psychosis. Cardiovascular autonomic dysfunction in PD can include a reversed or lack of blood pressure (BP) circadian rhythm, referred to as nocturnal non-dipping. The aim of this study was to determine the relationship between 24 hr ambulatory blood pressure measurements (ABPM), e.g., absence or presence of nocturnal dipping, and psychosis scores in PD.

Methods: 21 patients with Parkinson's disease underwent 24 hr ABPM using an autonomic protocol. A decrease in nocturnal mean arterial blood pressure (MAP) of less than 10% was defined as non-dipping. Patients were interviewed (including the Brief Psychiatric Rating Scale; BPRS) for the assessment of psychosis.

Results: 11 patients were dippers and 10 were non-dippers. BPRS scores were higher in non-dippers who on average met the criteria for psychosis (mean non-dipper BPRS: 34.3± 7,3 vs mean dipper BPRS: 27.5 ±5,3; cut off for "mildly ill" 31). There was a correlation between BPRS scores and non-dipping, indicating that those patients who had a blunted nocturnal fall in BP were more prone to psychotic symptoms.(Pearson's Correlation = .554, p =.009).

Conclusion: These results suggest that a blunted BP rhythm in Parkinson's disease patients may possibly be associated with psychosis symptoms compared to patients whose BP decreases physiologically at night. This association warrants further investigation.

Introduction

The cardinal features of Parkinson's disease include rigidity, bradykinesia, resting tremor and postural instability.[1] Non-motor symptoms are also being increasingly recognized in PD, such as neuropsychiatric symptoms and autonomic dysfunction amongst others, and are often the main cause of disability having a significant impact on quality of life[2] and are quite frequently the reason patients are moved to nursing homes[3]. Cardiovascular symptoms are typical features of an impaired autonomic nervous system. These include orthostatic hypotension[4], or a loss of the circadian rhythm of blood pressure, characterized by 'non-dipping'[5]; defined as a blunted, or absent decrease in blood pressure while sleeping at night.[6]

The human body is tuned to an (approximately) 24h rhythm, which is inter alia aligned by light and dark cycles. Circadian rhythms help with the entrainment of various key daily activities and functions, such as, sleep patterns, alertness, physical strength, blood pressure and even mood.[7] Twenty-four hour patterns and any associated circadian dysrhythmia, particularly an impaired blood pressure rhythm, have recently become of great interest to clinicians[8]. A blunted or even a reversed blood pressure circadian rhythm (e.g. non-dipping) is associated with end organ damage[9] and higher cardiovascular morbidity[10]. Furthermore, it has been suggested that non-dipping is also associated with other non-cardiovascular symptoms such as psychosocial factors.[11]

Non-dipping is common in PD, and ranges in prevalence from 40%[12] to 92%[13]. The reasons for a blunted/reversed circadian blood pressure rhythm in PD can include several factors, including pathological entities, such as disorders of nocturnal movement, obstructive sleep apnea (OSAS), supine hypertension and reduced quality of sleep.[14] Numerous other factors can influence blood pressure profiles at night, such as getting up at night secondary to urinary urgency or nocturia (both common in PD).

Psychiatric illnesses, such as psychosis (an abnormal condition of the mind, which involves a loss of contact with reality[15]), have also been linked with abnormal circadian blood pressure regulation.[16] Patients with psychosis are at higher risk of developing cardio-metabolic risk factors such as hypertension[17]. Up to 40 %[18] to 60%[19] of PD patients suffer from psychosis and 50% of PD patients will suffer from hallucinations (spontaneous aberrant perceptions without a physical stimulus[20]) in the course of the disease.[18] The link between abnormal circadian blood pressure regulation and psychosis in PD has not been specifically examined however. Such investigations are difficult, due to the number of factors that may contribute to psychosis in PD. For example, one of the most significant side effects of levodopa is psychosis[21] but only 16% of patients with dopamine agonist or levodopa medications develop drug-induced psychosis.[18] Other causes of psychosis could be low quality of sleep[22], which is however also likely to cause non-dipping.[14] Up to 90% of PD patients suffer from sleep disruption [23, 24] which may be caused by the hallmark PD pathophysiology of dopamine depletion which plays a crucial role in sleep regulation and circadian homeostasis[23].

The aim of this study was to therefore determine the relationship between 24 hr ambulatory blood pressure measurements (ABPM), e.g., absence or presence of nocturnal dipping, and psychosis parameters in Parkinson's disease, while also considering factors that could influence psychosis scores and non-dipping, such as quality of sleep, orthostatic hypotension, levodopa medication and severity/stage of Parkinson's disease.

Methods

Participants

A total of 21 patients who met the diagnostic PD criteria of the Queen Square Brain Bank[25] were included in this study, which was approved by the ethics committee of the University of Witten/Herdecke and the London, Camden & Islington NRES committee. Patients who had symptoms suggestive of atypical PD or any other diagnosis than idiopathic PD were excluded. Further exclusion criteria were diabetes and hypertension (or use of antihypertensive medication or other medication that could interfere with cardiovascular autonomic function screening, e.g., head up tilting, and 24 hr ABPM results). None of the patients were on anti-psychotic medication; only one patient was on anti-depressants (mirtazapine 15 mg.) All participants gave verbal and written informed consent prior to the start of any testing. All procedures were in line with the Declaration of Helsinki.

Protocol and Instrumentation

Patients reported to the Unit in the morning in the "off" stage, having been asked to skip the morning dose of their anti-PD medication. Patients were first assessed with a range of PD instruments, namely the Unified Parkinson's Disease Rating scale (UPDRS) [26] including the Hoehn and Yahr Scale[27], Schwab and England activities of daily living scale and the Parkinson's Disease Questionnaire (PDQ)[28]. These instruments were complemented with the mini mental state examination (MMSE). Additionally, two instruments to assess psychosis in PD patients[29] were administered: the brief psychiatric rating scale (BPRS) which usually assesses psychopathology in patients with schizophrenia[30], and the positive and negative syndrome scale (PANSS) which usually measures symptoms severity in patients with schizophrenia[31], both instruments are however recommended for use with PD patients.[29]

Every patient underwent a head-up tilt test to 60 degrees to ascertain whether or not they met criteria for OH.[6] which was defined as a reduction of systolic blood pressure of at least 20 mm Hg or 10 mm Hg in diastolic blood pressure within 3 minutes of quiet standing.[32] Afterwards, patients were fitted with an ambulatory blood pressure monitor (model 90207, Spacelabs™ Medical, Redmond, Washington) and instructed on how to use it appropriately. Automated blood pressure measurements were taken every 30 minutes during day time (07.00-23.00) and every 60 minutes at night (23.00-07.00).[33] Furthermore, patients were provided with a diary and asked to fill in daily events over the 24 hours, including, sleep and wake times, meal times or other food/caffeine intake, time of medications and posture (lying down, sitting, standing, walking, exercising) and activity at the time of every reading. Additional information, such as symptoms or emotional strain, was also requested to be noted in the diary. Participants were also asked to briefly evaluate their quality of sleep and if they got up during the night and if so, for what reason.

Statistical Analyses

Mean arterial blood pressure was calculated by [(2 x diastolic)+systolic blood pressure] / 3.[34] A normal circadian blood pressure profile was defined as a reduction in night time (asleep) mean arterial blood pressure by at least 10%

from the daytime (awake) mean arterial BP[6], otherwise known as ‘dipping’. A ‘non-dipping’ circadian BP profile was defined as a reduction in night time (asleep) mean arterial blood pressure of less than 10% from the daytime (awake) mean arterial BP.[6]A reversed nocturnal BP profile, e.g., an increase at night, was defined as an increase in night time (asleep) mean arterial blood pressure by at least 1% from daytime (awake) mean arterial BP.[35]

Indices of circadian blood pressure rhythm (e.g., daytime vs night-time mean values) were compared for the whole group using paired t-tests. Patients who met the criteria for dipper vs non-dipper were split into sub-groups and were compared using independent t-tests for equality of means (with Levene’s test for equality of variances) or Mann Whitney U tests, where appropriate. Levodopa equivalent dose (LED), a standardized conversion factor for total daily anti-parkinsonian drug intake, was calculated following the guidelines of Tomlinson et al (2010).[36]

The relationships between indices of psychosis and dipping were assessed using Pearson product-moment correlation coefficients or Spearman rank order correlations (rho), where appropriate. Preliminary analysis was performed to ensure no violations of the assumptions of normality, linearity and homoscedasticity. The evaluation of relationship strength was defined by Cohen as small: r=.10 to .29; medium: r=.30 to 49;large: r=.50 to 1.0.[37] Indices of psychosis were also correlated with LED, age, disease duration, PDQ, UPDRS, gender, OH and sleep quality. The level of significance was set at 0.05. Data are presented as mean ± 1 standard deviation.

Results

Participant details

21 patients with PD (15 male, 6 female) were recruited. The average age was 63.9 (±7.6) years and mean disease duration (calculated from the time of diagnosis) was 6.6 (±7.0) years. Patients had a mean UPDRS Score of 28 (±13) and 38 % were in Hoehn & Yahr stage I, 52% in stage II and 10% in stage III. None of the participants had an MMSE score below 28, except for one (MMSE 21) (See Table 1).The mean LED was 423 (±431) mg. The high standard deviation was caused by 2 outliers, one of which was due to the patient refusing not to take their anti-parkinsonian medication on the day of testing. When the outliers were excluded, a mean LED of 359±254 mg was evident. The median LED was 200 mg. Only two patients showed orthostatic hypotension (OH), on average, systolic blood pressure fell by 9.7±14 mmHg (-7± 9%) during head up tilt.

Ambulatory BP and Psychosis Data

Ambulatory BP was recorded for a mean duration of 23.8 (±2.4,range 19.0-28.5) hours. The average number of measurements obtained in the ~24 h period was 42 (SD 13, range: 26-80). The average amount of sleep at night was 7.1 hr (±1.8, range: 4-11). 28.5% of patients stated that their quality of sleep was not satisfactory, whilst another 28.5% (not necessarily the same patients) had to get up at night (e.g. in order to use the bathroom).

The mean daytime systolic blood pressure was 125 (± 11) mmHg and the mean nighttime systolic blood pressure was 117 (±14) mmHg (see Table 2). 47.6% of the patients displayed a non-dipping 24hr BP profile, 3 of which displayed a reversed circadian blood pressure rhythm. 11 patients were dippers (52.4%).

A BPRS score over 31 is considered as ‘mildly ill’, a score over 41 as ‘moderately ill’ and a score over 53 as ‘markedly ill’[30]. 12 patients (57%) scored over 31, of which, 2 were over 41. When analyzing the PANSS, a score of 51 and above was considered ‘mildly ill’[38], which none of the patients reached. The BPRS and PANSS scores were highly correlated (Pearson’s R = 0.89; p <.0001).

Sub-group Analyses

The sub-groups of non-dippers vs dippers did not significantly differ in age (t_{19} = .137, p = .893), disease duration (t_{19} = -2.039, p= .056), LED (t_{19} = .757, p= .458) or UPDRS scores (t_{19} = -2.078, p= .052). Furthermore, no difference in gender was found (p=.484; Z=-.701). There was no difference in sleep duration for dippers vs. non-dippers (p=.137; Z=111.5). 30% of the non-dipper patients reported a bad quality of sleep, compared to 27% of the dippers. On HUT, non-dippers exhibited a mean fall in SBP of 13 (± 11) mmHg whereas dippers exhibited a decrease of 7 (± 17) mmHg (see Table 1).

BPRS scores were higher in non-dippers who on average met the criteria for mild psychosis (non-dipper BPRS: 34.3± 7.3 vs. dipper BPRS: 27.5 ±5.3, p= 0.009; see Table 1). All non-dippers, except one, met (at least) the criteria for mild psychosis (PANSS data is depicted in Table 1). There was no difference in BPRS scores (p=.911; Z=-.112)

or night time MAP (p=.654; Z=-.448) when comparing those who did and did not sleep well in both dipper and non-dipper groups.

Correlations

There was a strong (large) correlation between BPRS and dipping in the whole group (Pearsons r: 0.554, p=.009;see Figure 1). The correlation between PANSS scores and dipping was weaker, with a medium correlation (Pearsons r: 0.394, p=.077). When investigating other factors associated with dipping/non-dipping, only 3 were found to be correlated (of medium strength); UPDRS scores (Pearson's r: .491, p=.024), OH (Pearson's r: .437, p=.048) and disease duration (see Table 3).

For factors influencing BPRS scores, two statistically significant relationships were evident (see Table 3). PDQ (Pearson's r: .58, p=.01) (Figure 2), and UPDRS scores (Pearson's r: .48, p=.03) correlated with psychosis. LED scores did not correlate with BPRS scores (r:-247, p=.292).

Discussion

The aim of this study was to determine the relationship between 24 hr ambulatory blood pressure measurements (ABPM), e.g., absence or presence of nocturnal dipping, and psychosis parameters in Parkinson's disease, while also considering confounding factors that could affect psychosis scores and non-dipping.

The percentage of non-dipping in this sample was 47.6 %, which falls into the broad prevalence range of 40%[12] to 92%[13] described in the literature. 57% of the PD patients met the criteria for mild psychosis symptoms, which is consistent with previous literature which described a psychosis prevalence of 40%[18] - 60%[19] in PD. PANSS scores were correlated strongly with BPRS scores, but none of the patients met the criteria for psychosis according to the PANSS (i.e. had scores over 51). This implies that the BPRS is more sensitive in detecting psychosis symptoms (at least in PD patients). This could be derived from the fact that the PANSS covers more symptoms of psychosis (30 items compared to 18 in the BPRS). It has to be considered though, that two of the 18 BPRS items consider motor retardation and mannerism/posturing, which are all symptoms that may be evident in PD patients, and not necessarily[39] but possibly linked to psychological symptoms.[40] This might therefore artificially raise psychosis scores in PD patients, even though both instruments are recommended by the Movement Disorder Society Taskforce.[29]

The mechanisms of non-dipping in PD are not entirely clear. PD is pathologically characterized by neuronal cell loss with deposition of abnormally phosphorylated α-synuclein, found in Lewy bodies.[41, 42] Degeneration with Lewy bodies are not only found in the substantia nigra but also in the brainstem nuclei (e.g. pedunculopontine nucleus) essential for thalamocortical arousal and therefore REM sleep architecture[43]. Furthermore, Lewy bodies can be found in autonomic regulatory areas, such as the parabrachial nucleus, neurons in paravertebral and paravertebral autonomic ganglia, hypothalamus.[42] Interestingly, the suprachiasmatic nuclei, which controls circadian rhythms in humans lies in the hypothalamus[14], whether this exact part of the hypothalamus is affected by lewy bodies remains unclear however. It is therefore possible that the above mentioned aspects of PD pathology in key autonomic and circadian areas of the brain might also affect circadian rhythm regulation of blood pressure.

The absence of circadian BP dipping was associated with OH, disease duration and UPDRS scores. The former is also a symptom of an impaired cardiovascular autonomic nervous system, and was thus not unexpected; although only 2 patients met the clinical criteria for OH (correlation was conducted with scale data). Previous studies have reported an association with OH and supine hypertension[44] which could serve as an explanation for non-dipping in PD. The association of non-dipping with UPDRS scores is also not surprising given that cardiovascular symptoms are scored as part of the UPDRS and that cardiovascular autonomic dysfunction generally tends to occur in the latter stages of PD.[42]

Statistically significant differences in BPRS scores were found when comparing patients showing a non-dipping or dipping 24hr BP profile. Furthermore, a positive correlation between psychosis parameters and non-dipping was evident, indicating that the smaller magnitude of dipping (i.e. -10% and less) the more likely patients were to have higher BPRS scores. Both non-dipper vs. dipper patients, as well as patients with a BPRS above and below the cut-off of 31, did not differ significantly in age, gender, disease duration or UPDRS scores.

Since a correlation does not necessarily imply causation, several factors have to be considered when interpreting the correlation between dipping and BPRS data, such as the influence of sleep quality and duration, age, gender, levodopa medication, PD severity/stage of the disease. Low quality of sleep may cause non-dipping, due to agitation or similar symptoms of sleep deprivation,[14] which may furthermore cause psychosis.[22] Yet no difference in sleep duration for dippers vs. non-dippers was found in this study. However, a more robust sleep quality instrument such as the Pittsburgh sleep quality index (PSQI)[45] and/or objective sleep laboratory measurements might have given better insight into sleep quality.

Levodopa may induce psychosis and could possibly also have an effect on circadian rhythms.[21, 46] We did not find a statistically significant correlation between LED and psychosis scores or non-dipping.

The only significant associations with psychosis (apart from dipping) were for PDQ and UPDRS scores, which measure quality of life and disease severity, respectively. This could be interpreted as patients with more severe PD symptoms and impaired quality of life tending to have higher psychosis indices. An increased impairment in quality of life in those PD patients with a higher psychosis score may also indicate that these patients have a more severe subjective perception of illness. The significant correlation between UPDRS and psychosis could be a reflection of PD pathology affecting psychosocial function (see below).

The mechanisms of how non-dipping may be associated with psychosis remain elusive. A possible mechanism might be related to dopamine which is a common neurotransmitter related to psychosis and circadian rhythms[47] and of course to PD pathology [48] and could therefore be a plausible link between the three entities. The role of dopamine in psychosis and PD has been well studied[48-50] but is also gaining increasing awareness within the field of circadian rhythm disruption.[47] A link between schizophrenia and sleep and circadian rhythm disruptions (SCRD) via common neurotransmitters such as dopamine has already been proposed.[43] An explanation for this would be that dopamine mediates the relationship between psychosis and Cholecystokinin (CCK), a peptide hormone, which possibly plays a role in sleep regulation[47]. CCK furthermore activates orexin, a neurotransmitter that has an effect on wakefulness.[47]

It however remains unclear if a similar association exists within PD. The reasons for a causation between a pathological loss of the nocturnal BP fall and psychological symptoms in PD warrants further evaluation.

In conclusion, 24 hr ABPM revealed that non-dipping BP profiles in PD patients were associated with higher psychosis scores than in those patients whose BP drops physiologically at night. No other factors, except disease severity scores (PDQ and UPDRS), in this sample of patients were found to influence the psychosis scores.

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Author Roles:

CAH conceived the initial idea to the project, CAH, ES, DAL and CJM managed the ethics committee application, ES, EV, DAL and CAH contributed to the Conception, Organization and Execution of the Research project, ES and EV performed all testing, CAH, CJM, DAL and SI supervised the project. ES, EV, DAL and CAH contributed to the Review and Critique of the Statistical Analysis, ES drafted the original version of the manuscript, DAL, EV, CJM, SI and CAH contributed the Review and Critique of the Manuscript. All authors contributed extensively to the work presented in this paper

Full financial disclosure of all authors for the past year:

Stock Ownership in medically-related fields	Intellectual Property Rights
Consultancies	Expert Testimony
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Partnerships	Contracts
Honoraria	Royalties
Grants	Other

Figure Legends

Figure 1: Scatterplot of Nocturnal MAP dipping and BPRS scores in the whole patient sample. The short-dashed horizontal line indicates the horizontal cut-off for psychosis (BPRS score of 31). The dashed vertical line indicates the cut off for non-dipping (10%).The correlation is r - 0.55 (p =.009).

Figure 2: Scatterplot of PDQ and BPRS scores in the whole patient sample. The dashed vertical line indicates the horizontal cut-off for psychosis (BPRS score of 31). The correlation was r= .583 (P=.006).

Table 1: Overview of Dipper and Non-Dipper sub-group data (mean (SD).

Table 2: Overview of mean (SD) 24 hr ABPM data; BP in mmHg, HR in beats.min^{-1}, P<0.05 vs daytime

Table 3: Overview of correlations (R (p value)) between BPRS and Dipping and various cardiovascular, medical history, medication and disease severity

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