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Heart rate circadian profile in the differential diagnosis between Parkinson disease and multiple system atrophy

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ABSTRACT

Clinical diagnostic criteria indicate presence of autonomic features as the primary hallmark of Multiple System Atrophy (MSA). However involvement of the autonomic system is also a recognized feature of Parkinson's Disease (PD), yielding a broad clinical overlap between the two diseases. Laboratory assessments may help in the differential diagnosis between PD and MSA. Ambulatory Monitoring of Blood Pressure (AMBP) is a suitable tool to study the circadian rhythm of blood pressure (BP) and heart rate (HR). Different studies reported a reduction of physiological BP nocturnal dipping in PD and MSA patients, but failed to identify a distinctive pattern discriminating the two diseases. On the other hand, HR nocturnal behavior has not been exhaustively analyzed. In the present study we compared the profiles of HR circadian rhythm in 61 PD and 19 MSA patients who underwent 24 h AMBP.

We found higher nocturnal HR (nHR) (71.5 beats/min ± 7.4) in MSA compared with PD (63.8 beats/min ± 9.6) as well as significantly lower nocturnal decline of HR (ndHR) in MSA (7.3% ± 8.2) vs. PD (14% ± 7.5). At a Receiver Operating Curve analysis nHR and ndHR significantly discriminated MSA from PD. nHR showed a sensitivity of 84.2% and a specificity of 62.3% (AUC 0.76; 95% IC 0.65–0.85); ndHR showed a sensitivity of 68% of and a specificity of 77% (AUC 0.72; 95% IC 0.61–0.82).

According to our findings, nHR is increased and ndHR is reduced in MSA compared to PD. Moreover, these two indices discriminate between the two diseases with acceptable accuracy.

1. Background

An accurate differential diagnosis between PD and MSA is extremely relevant for its prognostic and therapeutic implications but discrimination of the two diseases is oftentimes challenging due to their broad clinical overlap. According to clinical diagnostic criteria, autonomic symptoms, namely orthostatic hypotension, urinary and erectile dysfunction are the primary hallmark of MSA [1,2]. However, involvement of the autonomic system is now a well-recognized feature also in PD, even at the early stages of the disease [3].

Litvan et al., retrospectively applied clinical diagnostic criteria for MSA to autopsy-confirmed cases, showing "suboptimal" sensitivity and specificity [4] Successively revised clinical criteria [1,2] improved diagnostic accuracy [5] It has been suggested that inclusion of laboratory tests may help detecting and characterizing autonomic dysfunction [6] which, in turn, increases the reliability of clinical diagnosis [7,8].

The composite autonomic severity score (CASS), resulting from 10 autonomic tests exploring sudomotor, adrenergic, and cardiovagal function may differentiate PD from MSA [7,8]. Nevertheless many of the tests required to obtain CASS can be performed only in specialized laboratories.

Ambulatory BP monitoring (ABPM) is a broadly available tool for the assessment of cardiovascular autonomic control [9]. Disruption of circadian variations of BP, characterized by loss of physiological BP nocturnal decline (non dipping pattern) or BP nocturnal increase (reverse dipping pattern), has been described in PD [9] MSA and PSP patients [10]. Comparison of BP profile revealed reduced BP nocturnal decline in MSA, compared with PD and PSP patients; this index significantly discriminated between MSA and PSP, but not between MSA and PD [11].

Reduced nocturnal physiologic decline of HR has also been reported in different extrapyramidal diseases compared to healthy

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controls [10], but nocturnal HR patterns in MSA and PD have not been exhaustively investigated.

The aim of the present study is to assess the discriminating ability of nocturnal HR modifications in PD and MSA patients.

2. Methods

This is an observational, cross-sectional, comparative study. The protocol was approved by Local Ethical Committee of San Camillo Hospital and was conducted in the respect of the guidelines for good clinical practice for experimental trials in human beings.

Eighty-six consecutive patients with diagnosis of PD or MSA, were included. Diagnosis of PD and MSA was formulated according to validated clinical criteria, namely London Brain Bank Criteria for PD [13] and Second Consensus diagnostic criteria for MSA [2].

Clinical diagnosis was defined through exhaustive anamnesis and neurological examination. All patients with the exception of one who suffered of claustrophobia had 1.5T magnetic resonance imaging. All patients complaining about urinary disturbances underwent urologic evaluation and uroflowmetry. Dysfagia and dysartria, whenever reported by the patients, were evaluated by logopedic and phoniatric assessment.

Disease stage was stated by the Hoehn and Yahr (H&Y) scale while motor impairment was evaluated by means of the validated Italian version of the MDS-UPDRS scale [14]. Dopaminergic medications were recorded, and the Levodopa Equivalent Daily Dose (LEDD) was calculated according with previously published formula [15]. Co-morbidities were recorded, paying special attention to clinical history of cardiovascular disease. Concomitant medications which could potentially affect HR, such as therapies active on cardiovascular system, were also recorded.

All patients underwent ABPM, for 24 h monitoring of Systolic BP (SBP) Diastolic BP (DBP) and HR, recorded by a validated system (BP ONE, Righetto-Italy) during patient's normal daily activities and nocturnal rest, according to international guidelines [16].

The sphygmomanometer cuff was placed on the non-dominant arm and the recording system was programmed to obtain measurements at 30-min intervals during day time (from 8 AM to 9 PM) and at 60 min intervals during night time (from 10 PM to 9 AM). Evaluations with a minimum of 75% of records available and compatible with physiological values were considered acceptable for data analysis.

Diurnal, nocturnal and 24 h SBP, DBP and HR were calculated from the average of the records of each parameter registered in the respective periods. The amount of nocturnal variation, was calculated for each parameter according to the following formula: (diurnal value-nocturnal value/diurnal value) $\times$ 100, and expressed as a percentage.

According to published criteria [17], patients were classified in three groups based on the pattern of nocturnal variation of SBP:

1) BP dippers: patients with $\geq$10% decline of mean SBP during night time; 2) BP non-dippers: patients with a nocturnal decline of mean SBP $<$ 10%; 3) BP reverse dippers: patients with an increase of SBP during night time.

Nocturnal hypertension was defined according to the guidelines of the American Hypertension Association (SBP $>$ 120 mmHg and DBP $>$ 75 mmHg) [13].

Arterial hypotension was defined according to World Health Organization criteria (SBP ranging between 110 mmHg in males and 100 mmHg in women, regardless diastolic value) [18].

3. Statistical analysis

SPSS software package version 16.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical evaluations. Continuous data are presented as mean and standard deviation. Between group comparison was performed by Student *t*-test for all demographic and clinical parameters. ANCOVA test, corrected for age, disease duration and LDED was performed to compare all ABPM parameters in the two groups. For those indices resulting significantly different (ANCOVA test), a Receiver Operator Curve analysis (ROC) was performed to determine their sensitivity and sensibility in discriminating between PD and MSA.

Nominal data were compared by Fisher exact test.

The level of statistical significance was set at $P < 0.05$.

4. Results

Sixty-four patients had PD and 22 MSA.

Eighty AMBP records (61 of the PD and 19 of the MSA group) were considered reliable and were used for data analysis. Among the 19 MSA patients, 16 had a diagnosis of probable MSA and three of possible MSA.

MSA patients presented shorter disease duration, higher disease stage and severity and lower LEDD compared with PD. Demographic and clinical data are reported in Table 1.

Six MSA and 21 PD patients were on anti-hypertensive drugs. Two patients (10%) in the MSA and 4 (6%) in the PD cohort were taking medications with marked chronotropic effect on HR, such as beta-blockers but none was on alfa-blockers. Three MSA patients and 2 PD patients were taking day time administrations of midodrine for orthostatic hypotension.

The results of ABPM are reported in Table 2. Abnormalities of circadian BP rhythm were observed in 88% of PD and 94% of MSA patients. Among PD, 20 (33%) were non dippers and 34 (55%) were reverse dippers. Among MSA, 6 (31%) were non dippers and 12 (63%) were reverse dippers. Nocturnal hypertension was recorded in 10 MSA patients (19%) and 15 PD patients (24%).

Twelve MSA (63%) and 18 PD patients (29%) presented at least one episode of diurnal hypotension during ABPM recording.

Mean 24H, diurnal and nocturnal BP values did not significantly differ between PD and MSA. Nocturnal variation of SBP and DBP was also similar in the two groups. Nocturnal HR (nHR) was significantly higher in MSA (71.6 $\pm$ 7.46 beats/min) than in PD (63.8 $\pm$ 9.63 beats/min); MSA patients showed lower HR nocturnal decline (ndHR) (7.4% $\pm$ 8.23) compared to PD patients (14.1% $\pm$ 7.54) (Fig 1). These differences persisted after correction for age, disease duration and LEDD.

The ROC analysis revealed that nHR significantly discriminated MSA from PD, with a sensitivity of 84.2% (95% IC 60.5–96.6), a specificity of 62.3% (95% IC 49.0–74.4) and an AUC of 0.76 (95% IC 0.65–0.85) at a cut off of 65 beats/min; ndHR revealed a sensitivity of 68.4% (95% IC 43.4–87.4) and a specificity of 77% (95% IC 64.5–86.8) with an AUC 0.72 (95% IC 0.61–0.82) at a cut off of 8.86%. ROC curves are reported in Fig 2. After exclusion of patients on beta-

Table 1
Demographical and clinical data of patients.

	PD	MSA
	Mean (SD)	Mean (SD)
Age (years)	65.6 (9.31)	66 (7.77)
Disease duration (years)	11.7 (4.58)	4.9 (3.10)*
LDED (mg)	969 (382.27)	630.1 (300.53)*
DAED (mg)	151 (105.36)	88.9 (95.12)*
H&Y	2.8 (0.55)	3.5 (0.62)*
MDS-UPDRS motor part	36.2 (14.6)	62.8 (36.7)*

LDED: Levodopa Equivalent Daily Dose; DAED: dopamine agonists equivalent daily dose H&Y: Hoehn and Yahr Stage; MDS-UPDRS: Movement Disorders Society-Unified Parkinson Disease Rating Scale.
*$p < 0.01$.

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