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Intercepting Parkinson disease non-motor subtypes: A proof-of-principle study in a clinical setting

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ABSTRACT

The construct of non-motor symptoms (NMS) subtyping in Parkinson Disease (PD) is emerging as a line of research in the light of its potential role in etiopathological interpretation of PD heterogeneity.

Different approaches of NMS subtyping have been proposed: an anatomical model suggests that NMS aggregate according to the underpinning pathology; other researchers find aggregation of NMS according to the motor phenotype; the contribution of genetic background to NMS has also been assessed, primarily focusing on cognitive impairment.

We have analyzed NMS burden assessed through an extensive clinical and neuropsychological battery in 137 consecutive non-demented PD patients genotyped for MAPT haplotypes (H1/H1 vs H2 carriers) in order to explore the applicability of the "anatomo-clinical", "motor" or "genetic" models for subtyping PD in a clinical setting; a subsequent independent analysis was conducted to verify a possible cluster distribution of NMS. No clear-cut NMS profiles according to the previously described models emerged: in our population, the autonomic dysfunctions and depressive symptoms represent the leading determinant of NMS clusters, which seems to better fit with the hypothesis of a "neurotransmitter-based" model. Selective preferential neurotransmitter network dysfunctions may account for heterogeneity of PD and could address translational research.

1. Background

Parkinson's disease (PD) is a progressive neurodegenerative disorder, with proteiform clinical spectrum and scarcely predictable evolution [1]. A great effort has been engaged to define homogenous groups in order to intercept a pathophysiological coherence and prognostic trajectories of the disease [2]. In this term, non-motor domains remain integral for disease subtypes classification [1]. Indeed, non-motor symptoms (NMS) are theoretically significant in the context of etiopathological interpretations [3,4], complementary to the diagnostic procedure [5–7], relevant in disease managing [8–11] and likely determinant as a prognostic element [3].

Several studies of PD non-motor subtyping have been recently proposed in literature, mostly focusing on PD untreated patients. Some authors have postulated that certain symptoms tend to aggregate in specific clusters following an anatomo-clinical correlation [9]. According to this view, the occurrence of NMS clusters may be explained by the presence of different routes of degeneration that underlie the pathological process observed in PD. Based on this "anatomo-clinical model" [9], three main subtypes of non-motor profile have been identified: a brainstem subtype characterized by the prevalence of sleep and autonomic dysfunctions, a limbic variant with depression, fatigue and weight loss, and a cognitive subtype with a particular predominance of cholinergic dysfunctions such as memory impairment, apathy and anxiety.

Moreover, other groups have investigated the correlation between motor phenotypes and NMS profiles based on the empirical "motor model" and, though the results of all these studies are not univocal

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[10], they tend to suggest that the burden of NMS is more prominent in non tremor dominant and in postural instability and gait disorder phenotypes [12–15], thus delineating a possible linkage between motor and nonmotor severity.

Genetic background represents another issue of potential interest in the expression profile of PD NMS; to date, previous researches have mostly focused on cognitive decline [15,16]. Convergent data suggest a role for microtubule associated protein tau (MAPT) genotype in Parkinson's disease dementia (PDD) [17–19]. However, the possible association of MAPT genotype (H1/H1 homozygous vs H2 carriers) with the whole non-motor phenotypes has not yet been investigated, configuring a potential genetic background of NMS subtypes.

It remains to establish the practicality of the models of NMS aggregation ("anatomo-clinical", "motor" or "genetic") in common clinical settings. Therefore, our study aimed at testing whether in a sample of unselected PD patients NMS tend to aggregate according to the hypothesis of the "anatomo-clinical model", the motor phenotype or the genetic MAPT background. Furthermore, a subsequent analysis was conducted in order to verify a possible cluster distribution of NMS in our PD cohort.

2. Methods

2.1. Subjects

We enrolled consecutive PD outpatients from the Parkinson's Disease Unit of Sapienza University of Rome from September 2014 to August 2016. All subjects fulfilled the UK Brain Bank criteria for idiopathic PD [20]. Individuals were excluded if they had signs of atypical parkinsonism [21], dementia [22] and/or doubtful response to dopaminergic replacement therapy.

2.2. Patients assessment

We collected demographic data (age, gender and education) and neurological history (age at onset of PD, duration of disease and specific treatments).

All patients underwent a clinical and a neuropsychological examination and a genetic analysis.

2.3. Clinical evaluation

Three neurologists with expertise in movement disorders (MEDB, AR, PC) investigated PD patients using motor scales, such as Unified Parkinson's Disease Rating Scale (UPDRS) part III and V (Hoehn and Yahr Scale [H&Y]), freezing of gait questionnaire (FOG) and nonmotor scales, such as Non Motor Symptoms Scale (NMSS) to assess frequency and severity of a wide range of NMS [23], Autonomic Scale for Outcomes in Parkinson's disease-Motor (SCOPA-Aut) to evaluate dysautonomic dysfunctions and Epworth Sleepiness Scale (ESS) for the evaluation of sleep disturbances. Three main motor phenotypes were considered: tremor-dominant subtype (TD), non-tremor dominant subtype (NTD) and postural instability and gait disorder (PIGD) subtype [8,24].

2.4. Neuropsychological evaluation

Two neuropsychologists (CP, GA) administered the following scales to explore the cognitive and neuropsychiatric profile of the subjects: Montreal Cognitive Assessment (MoCA) to assess the cognitive status (orientation, memory, executive function, conceptualization and visuospatial functions) [25], Beck Depression Inventory (BDI) for depressive symptoms [26], Neuropsychiatric Inventory (NPI) to investigate the presence of psychotic symptoms, mood disorders as well as the occurrence of negative symptoms such as apathy.

Total lower scores correspond to worse cognitive performances for MoCa, whereas for BDI and NPI total score is directly proportional to the severity of the measured construct. Subscores of each scales have been collected.

2.5. Genetic analyses

Genomic DNA was extracted from a peripheral blood sample by standard methods. The MAPT haplotype was determined by testing for the presence of a 238-base pair between exons 9 and 10 (del-In9) which characterises a H1 haplotype, while its delection determine a H2 haplotype [27].

3. Data analysis

Data distribution was investigated by means of Kolmogorov–Smirnov (K-S) test to determine the appropriate use of parametric or non-parametric procedures; descriptive statistics were used for the characterization of the sample. To explore currently proposed NMS clusters of PD [9], we performed a correlation analysis of the following NMS: dysautonomic symptoms (total score of SCOPA aut) and sleep disorders and fatigue (sleep/fatigue domain of NMSS) in order to investigate a "brainstem variant", depression (total score of BDI) and anxiety and apathy (subscores of NPI) to investigate a "limbic variant", cognitive functions (total score of MOCA) and anxiety and apathy (subscores of NPI) to investigate a "cognitive variant". In order to reduce data originating from raw scores of several NMS scales (investigating some overlapping symptoms), we planned to perform a factor analysis. Such an analysis would be followed by a hierarchical cluster analysis using the factors identified as parameters. Statistical analyses were performed by means of the Statistical Package for the Social Sciences (SPSS 23, IBM Corp. 2016).

4. Results

One hundred and thirty-seven patients with PD were included in the study. Table 1 shows demographic, clinical characteristics and scores distribution of motor and non-motor scales of the whole sample. On the

Table 1
Demographic data and assessment of motor and non-motor symptoms in patients with Parkinson's disease (#137).

	Value
Age	69.1 ± 7.4 (47–86)
Age of onset	61.0 ± 7.5 (40–77)
Duration of disease	8.2 ± 4.5 (1–19)
Sex: F (%)	50 (36.5%)
Genetic profile: H1 homozygous (%)	82 (63.6%)
UPDRS III	17.9 ± 7.6 (4–44)
FOG	8.4 ± 6.2 (0–24)
H&Y	2.1 ± 0.6 (1–3)
1	19 (14.7%)
1.5	1 (0.8%)
2	72 (55.8%)
2.5	8 (6.2%)
3	29 (22.5%)
Tremor dominant (%)	45 (33.8%)
MoCA	22.6 ± 4.8 (9–30)
BDI	10.6 ± 8.3 (0–44)
NPI	11.6 ± 12.0 (0–64)
SCOPA aut	15.0 ± 8.2 (1–40)
ESS	6.3 ± 5.0 (0–24)
NMSS	44.9 ± 32.8 (1–193)

Data are expressed as mean ± standard deviation (range) except where indicated.
UPDRS III, Unified Parkinson's Disease Rating Scale part III; FOG, Freezing Of Gate questionnaire; H & Y, Hoen & Yahr scale; MoCA, Montreal Cognitive Assessment; BDI, Beck Depression Inventory; NPI, Neuropsychiatric Inventory; SCOPA-Aut, Autonomic Scale for Outcomes in Parkinson's disease-Motor; ESS, Epworth Sleepiness Scale; NMSS, Non Motor Symptoms Scale.