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White matter changes and the development of motor phenotypes in de novo Parkinson's Disease

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ABSTRACT

Background: Parkinson's Disease (PD) patients are usually divided into Tremor Dominant (TD) and Postural Instability/Gait Difficulty (PIGD) subtypes. The latter is characterized by axial motor symptoms and worse outcomes, possibly also because of comorbid white matter disease. Therefore, the current study investigated the importance of Age-Related White Matter Changes (ARWMCs) in the development of different PD motor phenotypes.
Methods: The present 4-year longitudinal study recruited 63 de novo PD patients, who underwent MRI at the time of the diagnosis to rate ARWMCs. Motor subtypes (PIGD or TD) were evaluated at baseline visit, and after 2 and 4 years. Age, gender, UPDRS part III total score, comorbidities and ARWMC total score were included in a mixed effect logistic regression model for repeated measures.
Results: The likelihood of being PIGD subtype during the study period was associated with higher ARWMC total score (OR = 2.743; 95%CI = 1.137–7.802), but not with age (OR = 0.967; 95%CI = 0.818–1.143), female gender (OR = 0.169; 95%CI = 0.014–1.970), UPDRS part III total score (OR = 1.942; 95%CI = 0.888–13.470), and comorbidities (OR = 2.979; 95%CI = 0.560–15.849).
Conclusion: Motor dysfunction in PD is apparently multifactorial and, in particular, comorbid white matter disease might concur in the development of axial impairment.

1. Introduction

The clinical presentation of Parkinson's Disease (PD) consists of a variety of both motor and non-motor symptoms. In particular, different motor phenotypes have been recognized and PD patients are usually divided into Tremor Dominant (TD) and Postural Instability/Gait Difficulty (PIGD) subtypes [1]. However, at the time of the diagnosis, up to one third of patients are categorized with an indeterminate motor subtype, as they do not display an overt motor phenotype and require a prolonged observation time to receive the appropriate clinical motor phenotyping [2,3].

Motor subtypes of PD represent different clinical and prognostic groups. Indeed, TD patients feature predominant tremor symptoms and a more benign course, whereas PIGD patients present axial motor impairment with postural instability, falls and freezing of gait [2], and generally have a faster motor, non-motor and cognitive progression [2,4].

Worth of note, abnormalities of balance and gait have widely been associated with white matter hyperintensities in the general population [5]. Therefore, it has been suggested that comorbid white matter disease might be an independent contributor to the PIGD phenotype in PD [6–10]. Moreover, cardiovascular risk factors have also been associated with the axial impairment in PD, probably, through determining white matter disease [10,11]. However, previous studies are affected by two main drawbacks: the cross-sectional design not allowing the evaluation of the predictive value of comorbid white matter disease, and the heterogeneity of the PD population enrolled, with variable disease duration and severity.

Therefore, the present 4-year prospective study aims at evaluating: 1) the comorbid presence of Age-Related White Matter Changes (ARWMCs) in a population of newly diagnosed, drug naïve PD patients;

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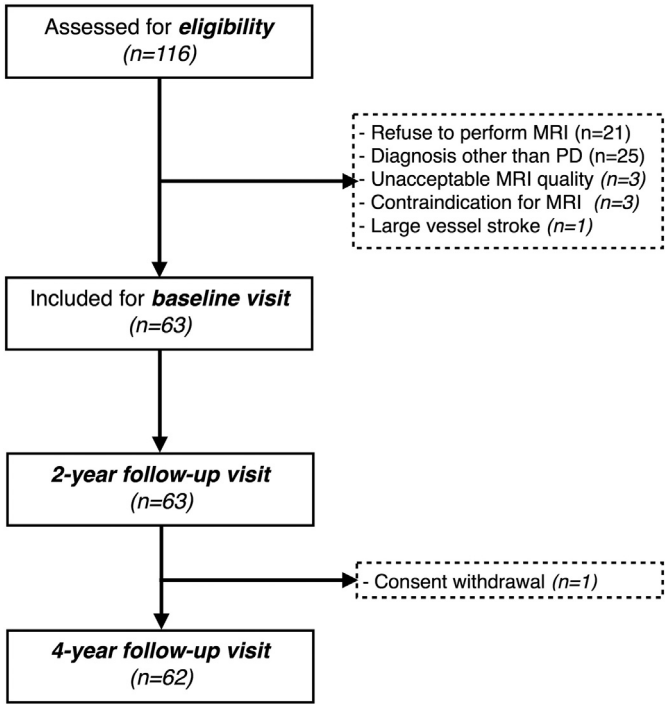

Fig. 1. Patient disposition flow diagram. Patient disposition flow diagram showing patients included, excluded or lost-to-follow-up.

2) the predictive value of ARWMCs in defining the motor phenotypes of PD during a 4-year prospective observation period; 3) the impact of comorbidities on the development of different motor subtypes.

2. Methods

2.1. Study design and population

The present observational cohort study rated ARWMCs in a population of de novo PD subjects at the time of the diagnosis, and prospectively evaluated their possible association with different motor subtypes during a 4-year period. The study was approved by the local Ethics Committee, and was performed in accordance with good clinical practices and the Declaration of Helsinki. All subjects gave informed consent.

PD patients were consecutively recruited at the Movement Disorder Unit, of the Federico II University Hospital (Naples, Italy), between January 2008 and June 2009. Inclusion criteria were: 1) diagnosis of PD according to the United Kingdom PD Society Brain Bank Diagnostic Criteria [12]; 2) reported symptom duration of less than 24 months; 3) no previous or current treatment with dopaminergic drugs.

Exclusion criteria were: 1) clinical diagnosis of vascular or atypical Parkinsonism, according to current diagnostic criteria [13]; 2) presence of large vessel stroke, striatal lacunar states or intracranial mass lesion at MRI [8]; 3) contraindication for MRI or unacceptable quality of the MRI scan (i.e. movement artifacts).

Patients with clinical signs suggestive of an alternative diagnosis at 2- and 4-year follow-up evaluations were also excluded.

Overall, from the original cohort of 116 patients, the reasons for exclusion from the present study were: refuse to perform MRI in accordance with study protocol (n = 21), diagnosis other than PD (n = 25), unacceptable quality of MRI (n = 3), contraindication for MRI (n = 3), large vessel stroke (n = 1), and consent withdrawal (n = 1) (Fig. 1).

2.2. Clinical evaluation

At baseline visit, demographic features and disease duration (expressed in months from the reported motor onset) were recorded. Motor symptoms and their impact on activities of daily living were evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS) part III and part II, respectively. UPDRS items for TD and PIGD designations were used to calculate mean TD and PIGD scores, as previously suggested [1], and the population was classified according to the motor subtype into TD, PIGD or indeterminate. Concomitant diseases and voluptuary habits associated with increased vascular risk (diabetes, hypertension, myocardial infarction, obesity, smoking) were recorded in order to calculate the comorbidity index, a measure of the disease burden, previously tested on general and neurological populations, including the present PD cohort [14,15].

Follow-up visits were performed after 24 ± 3 and 48 ± 3 months. UPDRS part III was evaluated during practically defined off-state (12 h off drugs), and UPDRS part II was collected. Subsequently, patients were categorized as being TD, PIGD or indeterminate at 2 and 4 year follow-up visits. Dopaminergic treatment was recorded and a total levodopa-equivalent daily dose (LEDD) was calculated [16].

During the 4-year follow-up period, clinical evaluations were performed by three neurologists (MM, RE, and MP), specifically trained and certified for UPDRS administration. Based on UPDRS recording, motor phenotyping was retrospectively performed in consensus by two experienced neurologists (MM, and MP), unaware of patients' past medical history and MRI evaluation.

2.3. MRI evaluation

All patients underwent an MRI scan of the brain at 1.5 Tesla (Philips GyroscanIntera), with an imaging protocol including axial Fast Spin-

Table 1
Demographics and clinical features of the PD population.
Demographics and clinical features of the PD population are reported from baseline visit, and 2- and 4-year follow-up evaluations. Results are shown as mean ± standard deviation (with range in brackets) or number (with % in brackets).

		Baseline (n = 63)	2-year visit (n = 63)	4-year visit (n = 62)
Age	Years	60.6 ± 13.5 (49–74)	–	–
Gender	Males	38 (60.3%)	–	–
Disease duration	Months	13.5 ± 5.4 (5–24)	–	–
Comorbidities	0	18 (28.6%)	–	–
	1	22 (34.9%)	–	–
	2	13 (20.7%)	–	–
	3 or more	10 (15.8%)	–	–
ARWMC total score		3.2 ± 2.9 (0 − 12)	–	–
UPDRS part III, off state		14.7 ± 8.1 (4–26)	19.3 ± 7.5 (6–35)	23.0 ± 6.2 (8–41)
LEDD		–	295.2 ± 123.7	456.5 ± 193.1
Motor subtype	PIGD	18 (28.6%)	20 (31.7%)	22 (35.5%)
	TD	27 (42.8%)	35 (55.5%)	36 (58.1%)
	Indeterminate	18 (28.6%)	8 (12.8%)	4 (6.4%)

PD: Parkinson's Disease; SD: Standard Deviation; ARWMC: Age-Related White Matter Change; UPDRS: Unified Parkinson's Disease Rating Scale; LEDD: L-Dopa Equivalent Daily Dose; PIGD: Postural Instability/Gait Difficulty; TD: Tremor Dominant.