Cluster of individuals with similar patterns of motor and non-motor symptoms in Parkinson's Disease: Potential therapeutic implications

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INTRODUCTION

Parkinson's disease (PD) presents a large variability in its progression and symptoms. This clinical heterogeneity allows to define PD subtypes from common characteristics of the patients[1] . The identification of homogeneous groups of patients with PD can help lead the research on future mechanisms of the disease and give rise to specific strategies for treatment[2].

OBJECTIVES

To identify homogeneous groups of PD patients according to the development of motor and non-motor symptoms throughout the time.

METHODS

►Observational, longitudinal (4 years) study of PD patients from ELEP study based on clinical assessment of motor and non-motor symptoms and disease severity by means of the scores obtained in validated scales (SCOPA-Motor, HADS, PPRS, SCOPA-Autonomic, SCOPA-Sleep, SCOPA-Psychosocial, SCOPA-Cognition, visual analogue scale (VAS) for measure pain and fatigue and severity of PD measure by CISI-PD). Evaluation scales were classified into four groups regarding the symptoms evaluated:

- **Motor symptoms:** SCOPA-Motor including subescales (motor examination, disability and complications) scores and VAS for fatigue;
- **Psychiatric non-motor symptoms:** HADS-Anxiety, HADS-Depression, PPRS, SCOPA- Psychocial, SCOPA-Sleep (including nighttime sleep and daytime sleepiness evaluation);
- **Non-psychiatric non-motor symptoms:** SCOPA-Autonomic, SCOPA-Cognition and VAS for pain and fatigue;
- **Disease severity:** CISI-PD.

►Higher scores of all scales indicate greater symptoms severity with the exception of SCOPA-Cognition, which is interpreted inversely (higher scores indicate better health status).

► In order to obtain classifications of patients into clinical subtypes according to the scores obtained in evaluation scales, a cluster analysis was performed in each group of symptoms together with disease severity as follows:

1. **Motor symptoms and severity;**
2. **Psychiatric non-motor symptoms and severity;**
3. **Non-psychiatric non-motor symptoms and severity.**

►Kml3D algorithm[3] was applied in the R statistical software[4] to clustering each group of scales. Kml3D is an R package based on the of k-means algorithm intended to clustering joint-trajectories (longitudinal data of continuous variables). The algorithm calculates 3 criteria to choose the optimal number of clusters (Calinski&Harabatz, Ray&Turi, Davies&Bouldin). In each partition into subtypes (clusters), the average of scales' joint-trajectories were obtained.

REFERENCES

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3. Genolini C, Pingault JB, Driss T et al.2013;109(1): 104-111.
4. Christophe Genolini (2012). R package version 2.1.2. http://CRAN.R-project.org/package=kml3d

RESULTS

Sociodemographic data

►174 patients were included in the analysis. 50% were men, 65% had primary or basic studies with a mean age of 63 years (DE: 11) and mean disease duration of 8 years (DE: 6) at inclusion.

►The main sociodemographic patients' characteristics during the 4 years were: married status, living in an urban habitat in their own home, not driving and not being member of a PD patients' association.

Cluster analysis of motor symptoms and severity

►The implementation of Kml3D algorithm indicate that the optimal number of subtypes of patients by motor symptoms and disease severity scales was 2, as maximum probability was 1 with the 3 established criteria **(Figure 1).**

► Considering the clinical characteristics related a motor symptoms and severity in each subtype of patients, subtype A patients had milder motor dysfunction and less severity disease than subtype B patients **(Table 1)** .

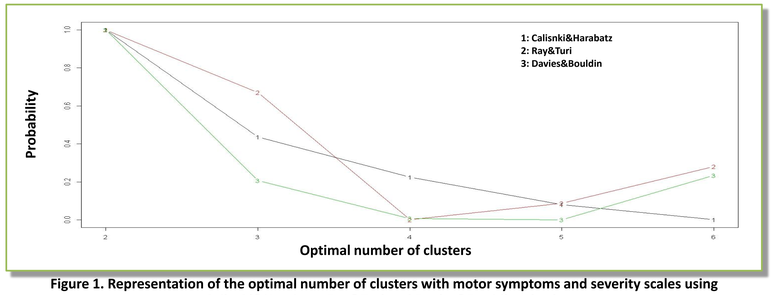

Figure 1. Representation of the optimal number of clusters with motor symptoms and severity scales using Calinski&Harabatz, Ray&Turi and Davies&Bouldin criteria

Table 1. Average of scales' joint-trajectories of cluster analysis of motor symptoms and severity

SUBTYPES	SCALES	YEAR 1	YEAR 2	YEAR 3	YEAR 4
SUBTYPE A (66.1% of patients)	SCOPA-Motor: Motor examination	6.22	6.56	6.67	7.23
	SCOPA-Motor: Disability	3.79	4.21	4.32	5.11
	SCOPA-Motor: Complications	1.21	1.22	1.22	1.96
	CISI-PD	5.48	5.45	6.03	6.97
	VAS Fatigue	19.99	23.01	27.40	29.64
SUBTYPE B (33.9% of patients)	SCOPA-Motor: Motor examination	9.66	10.41	10.90	11.81
	SCOPA-Motor: Disability	7.42	8.61	9.17	9.49
	SCOPA-Motor: Complications	4.20	4.19	4.41	4.51
	CISI-PD	10.56	11.17	11.88	12.49
	VAS Fatigue	35.74	42.40	42.46	41.46

Cluster analysis of psychiatric non-motor symptoms and severity

►The implementation of Kml3D algorithm indicate that the optimal number of subtypes of patients by psychiatric non-motor symptoms and disease severity scales was 2, as maximum probability was 1 with the 3 established criteria. **(Figure 2).**

►The clinical characteristics related to psychiatric non-motor symptoms from each subtype showed that subtype B patients had anxiety and depression, more severity disease and major problems of nighttime sleep **(Table 2)** .

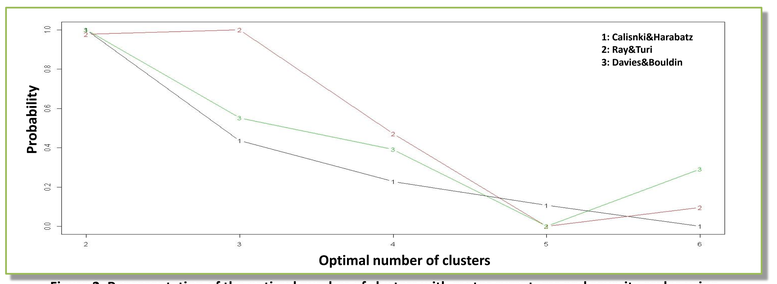

Figure 2. Representation of the optimal number of clusters with motor symptoms and severity scales using Calinski&Harabatz, Ray&Turi and Davies&Bouldin criteria

Table 2. Average of scales' joint-trajectories of cluster analysis of psychiatric non-motor symptoms and severity

SUBTYPES	SCALES	YEAR 1	YEAR 2	YEAR 3	YEAR 4
SUBTYPE A (56.3% of patients)	HADS Anxiety	5.21	5.03	5.31	5.37
	HADS Depression	3.64	3.82	4.14	4.22
	CISI-PD	5.80	5.62	6.24	7.37
	PPRS	0.63	0.52	0.75	0.79
	SCOPA-Psychosocial	3.78	4.50	5.13	5.31
	SCOPA-Sleep nighttime	4.59	4.39	4.55	4.28
	SCOPA-Sleep daytime	3.26	3.07	3.16	3.47
SUBTYPE B (43.7% of patients)	HADS Anxiety	9.90	9.84	9.70	9.28
	HADS Depression	7.63	8.45	8.51	8.12
	CISI-PD	9.07	9.65	10.30	10.74
	PPRS	1.38	1.24	1.57	1.64
	SCOPA-Psychosocial	10.81	12.41	12.06	11.86
	SCOPA-Sleep nighttime	6.67	6.07	5.84	5.38
	SCOPA-Sleep daytime	4.59	4.61	4.92	4.32

Cluster analysis of non-psychiatric non-motor symptoms and severity

►The implementation of Kml3D algorithm indicate that the optimal number of subtypes of patients by motor symptoms and disease severity scales was 2, as maximum probability was 1 with the 3 established criteria **(Figure 3).**

►The characteristics from each subtype showed that subtype B patients had major autonomic and cognitive dysfunction, more fatigue and pain and more severe stages of disease **(Table 3)**.

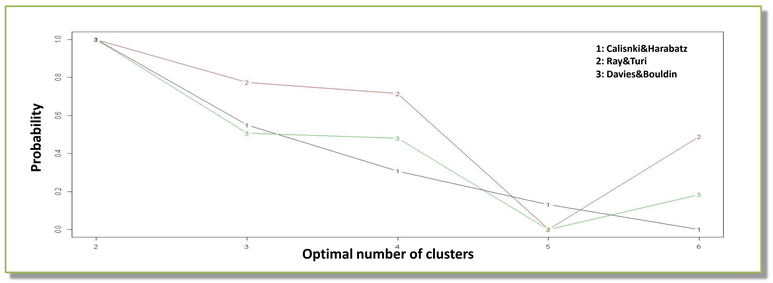

Figure 3. Representation of the optimal number of clusters with non-psychiatric non-motor symptoms and severity scales using Calinski&Harabatz, Ray&Turi and Davies&Bouldin criteria

Table 3. Average of scales' joint-trajectories of cluster analysis of non-psychiatric non-motor symptoms and severity

SUBTYPES	SCALES	YEAR 1	YEAR 2	YEAR 3	YEAR 4
SUBTYPE A (54.3% of patients)	CISI-PD	5.69	5.18	5.95	6.82
	SCOPA-Autonomic	16.09	21.81	21.50	18.61
	VAS Fatigue	16.16	17.07	21.39	28.02
	SCOPA-Cognition	27.34	27.79	27.90	27.48
	VAS Pain	12.91	10.72	13.55	19.58
SUBTYPE B (45.7% of patients)	CISI-PD	9.01	10.00	10.51	11.25
	SCOPA-Autonomic	26.22	34.39	34.65	27.00
	VAS Fatigue	35.94	44.47	45.65	40.27
	SCOPA-Cognition	21.81	20.70	19.90	20.67
	VAS Pain	26.57	27.16	26.18	27.10

CONCLUSIONS

The Kml3D algorithm identified two profiles of patients in the sample of the study characterized by mild differences in disease severity, motor dysfunction and dysautonomy throughout the four studied years. Together with motor dysfunction, non-motor symptoms allowed an approximation for characterizing this PD patients. Further analysis are required to establish the potential therapeutic implications in the sample of patients included in this study.