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Short communication

Clinical clusters and dopaminergic dysfunction in de-novo Parkinson disease

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ABSTRACT

Background: The heterogeneity of PD suggests the existence of different subtypes. While some motor clusters have been consistently identified, little is known about non-motor PD subtypes and motor-non-motor interplay. Research in this regard has produced somewhat contradictory results, which might be biased by the inclusion of treated patients.

Patients and methods: We performed a non-hierarchical cluster analysis using both motor and non-motor data on 398 newly diagnosed untreated PD patients enrolled in the Parkinson's Progressive Marker Initiative (PPMI) study. We further evaluated whether dopaminergic dysfunction, as measured by ^{123}[I]-FP-CIT SPECT scan, could explain, at least partially, the observed difference between the clusters.

Results: Three clusters were identified. Group 1 was characterized by the lowest motor and non-motor burden, whereas group 2 and 3 had similar motor disability, but different non-motor involvement, especially with regards to apathy and hallucinations. ^{123}[I]-FP-CIT binding values paralleled motor disability burden among the 3 clusters, but further multivariate analyses also revealed a negative correlation with depression.

Discussion: Our results confirm the motor as well as non-motor heterogeneity of PD, suggesting the existence of 3 different subtypes. Dopaminergic dysfunction only marginally explains the non-motor variability of PD. Identification of such clusters can have important implications for generating novel pathophysiological hypotheses and therapeutic strategies.

Attempts to subtype Parkinson disease (PD) patients have often used "data-driven" approaches and some motor clusters [e.g. tremor dominant (TD) versus postural instability/gait disorder (PIGD)] have thereby consistently been identified [1]. However, owing to the increasing evidence that non-motor symptoms (NMS) are integral to PD and can dominate the clinical picture in some patients [2], recent research has focused on the non-motor subtyping of PD [3–8]. Attempts to achieve this have produced somewhat contradictory results in terms of both the number of possible non-motor clusters [3–6] and motor-non-motor interplay [3–8]. The observed discrepancies may be due to methodological differences, including the nature of the cohorts, type and number of used variables, and presence of other confounding factors such as inclusion of treated patients. The latter issue might potentially represent a crucial bias in this context, since a number of NMS are induced and/or worsened by dopaminergic therapy [9]. Using data-driven approaches with newly diagnosed, untreated PD patients would not only overcome such a bias, but might also provide a framework to generate pathophysiological hypotheses able to explain the complex heterogeneity of PD.

In this study, we aimed to address this topic using a non-hierarchical cluster analysis (nHCA) including motor and non-

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motor data from the Parkinson Progressive Markers Initiative (PPMI) study. We further explored whether dopaminergic dysfunction, as measured by ^{123}[I]-FP-CIT, could explain, at least in part, the observed difference between the clusters.

1. Methods

Data used in the preparation of this article were obtained from the PPMI database (accessed on February 2015). For up-to-date information on the study, visit www.ppmi-info.org. The following clinical data were used for the statistical analyses: gender, age at onset, MDS-UPDRS part 3 (e.g. motor evaluation), Montreal Cognitive Assessment (MoCA), Geriatric Depression Scale (GDS), the State-Trait Anxiety Inventory for Adults (STAIT), the University of Pennsylvania Smell Identification Test (UPSIT), the REM Sleep Behavior Disorder Questionnaire (RBDSQ), and the Scales for Outcomes in Parkinson's Disease-Autonomic (SCOPA-AUT) with its sub-scores relative to each autonomic domain (e.g., gastrointestinal, urinary, cardiovascular, thermoregulatory, pupillomotor, and sexual). Moreover, tremor, bradykinesia, rigidity, and axial subscores were calculated from the MDS-UPDRS part 3 as previously described [10] and used for the analyses. Furthermore, presence of apathy, hallucinations, fatigue and pain were obtained from the MDS-UPDRS part 1 and also used for the nHCA. In order to help interpretation these four variables were later dichotomized considering whether symptoms were present or not when evaluating differences between the groups identified through the nHCA.

^{123}[I]-FP-CIT binding values were then compared between the identified clusters. Association between ^{123}[I]-FP-CIT binding values and each NMS was also explored.

1.1. Statistical analyses

The aforementioned variables were subjected to a non-hierarchical cluster analysis (k-means method) using the Gower method for mixed data (continuous and categorical data), for 3 to 6 cluster solutions. The Calinski-Harabasz pseudo-F value was used to assess when the clustering optimum solution was attained. To evaluate possible differences in the selected outcomes among the identified clusters post-hoc analyses including analysis of variance with subsequent Scheffé post hoc tests, Kruskal Wallis test with subsequent non-parametric Dunn's post hoc tests, Chi-square test and Fisher test were performed, as appropriate. ^{123}[I]-FP-CIT binding values were then compared among the identified clusters using analysis of variance with subsequent post-hoc tests as described above. Finally, multivariate linear regression models were used to explore the association between ^{123}[I]-FP-CIT binding values (as dependent variable) and each NMS, adjusting the models for age, gender, MDS-UPDRS part 3 and for a newly originated variable defining the identified clusters. For each model an interaction term between each NMS and the cluster variable was fitted to assess whether there was a difference in the relationship between ^{123}[I]-FP-CIT binding values and each NMS within the clusters. Results from regression models were presented as regression coefficient (coeff.) with 95% confidence intervals (CIs). Results were considered statistically significant if $p < 0.05$. Stata 12.0 was used for statistical analyses.

2. Results

A total of 398 newly diagnosed untreated PD patients without any missing values for clustering were included in the current study. The clustering optimum was attained for the 3 clusters solution (Calinski-Harabasz pseudo-F = 32.87). Table 1 details the mean values of all variables used for the nHCA, as well as the ^{123}[I]-FP-CIT binding values, among the 3 clusters. In summary, Group 1 was characterized by the lowest motor and non-motor burden, whereas group 2 and 3 had similar motor disability, but different non-motor involvement, especially with regards of apathy ($p < 0.01$), hallucinations ($p = 0.01$), fatigue ($p < 0.01$) and, possibly, cognitive impairment ($p = 0.052$).

As to the imaging findings, binding values paralleled the pattern of motor disability observed clinically, with group 1 having the higher scores (reflecting less nigral-striatal denervation) and group 2 and 3 showing similar values . Results from fully adjusted linear regression models showed that increasing GDS, for those in the third cluster as compared to the first, was associated with lower right caudate score (coeff −0.50 95%CIs −0.76–0.24), and lower mean striatum score (coeff. −0.28 95%CIs −0.45–0.99).

3. Discussion

Our study identified 3 clusters, which were profiled according to the presence and relevance of both motor and certain non-motor features. Whereas group 1 showed the lowest motor and non-motor burden, possibly indicating a benign subtype of PD, groups 2 and 3 displayed similar motor disability but differed from each other in the presence of additional non-motor features, including apathy and hallucinations (Fig. 1). Furthermore, a statistical trend was observed with regards to cognition ($p = 0.052$), indicating that patients belonging to group 2 might be more prone to develop cognitive impairment during the disease course. Our results reinforce the concept that attempts to dissect the heterogeneity of PD should in fact consider the presence and relevance of NMS [3], arguably as a function of non-dopaminergic system involvement.

It should be noted that nHCA depend heavily on the breadth and depth of the input variables used in the model. In this regard, one would argue that the disparity in the number of variables entered in the cluster analysis across different domains (e.g., autonomic domain vs cognition) could affect the weighting of the entire statistical model. While this is theoretically true, our results would argue it was not the case. In fact, no differences were found among the clusters as to dysautonomia, the domain for which the highest number of variables were available for clustering. Such a weighting issue might involve the motor features. To achieve a reasonable balance between quantity and quality of the motor information to provide, we entered in the model the total MDS-UPDRS3 score (reflecting the overall motor disability) and the combined subscores reflecting the severity of each cardinal motor PD sign (e.g, tremor, bradykinesia, rigidity and axial disability), largely in line with previous studies [1,5,6,10]. Nonetheless, previous studies using data-driven approaches have mainly addressed the variability of motor PD or focused on only one non-motor domain (e.g., cognition) [1]. Therefore comparisons with previously published clusters are not straightforward. However, our results bear resemblance to those recently published by Fereshtehnejad and colleagues [5] who, using both motor and non-motor prospective data of 113 treated patients, identified 3 clusters, the most critical determinants of PD variability and prognosis being cognitive status, RBD, and orthostatic hypotension (OH). In fact, they identified a “mainly motor/slow progression” cluster [5] that closely resembles our group 1, characterized by minimal motor disability and virtual absence of non-motor complications. At the other end of the spectrum, they identified a “diffuse/malignant” subtype, characterized by the presence of OH, poor cognition and RBD [5]. Although OH and RBD were not statistically different between our clusters (specifically, between group 2 and 3; Table 1), it is worth noting that Fereshtehnejad et al. used actual blood pressure drop values and data obtained from overnight polysomnography [5] whereas presence of OH and RBD in the PPMI cohort was inferred

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