Clustering of Parkinson Subtypes: Strong Influence of D2 Receptor Polymorphism and Gender

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Abstract

Next to motor and non-motor symptoms some more basic features are relevant in idiopathic Parkinson's disease subtype classification influencing basal ganglia circuitry via dopamine receptor polymorphism and gender dimorphism. By *kmeans*-clustering algorithm we found an influence of D2 receptor polymorphism and gender on treatment response to dopaminergic drugs -reflected by daily levodopa dosage- opening the door for a more personalized individual therapy in idiopathic Parkinson's disease.

Introduction

Parkinson's disease (PD) is next to Alzheimer's disease one of the most common neurodegenerative disorders[1]; it presents with heterogeneous clinical symptom courses[2] in the motor and non-motor domain. A classification into parkinsonian subtypes (as already suggested for the motor domain in akinetic-rigidic, mixed-type and tremor-dominant subtype[3]) is reasonable to better characterize the individual disease progression and further understand the underlying brain pathology. All these characterizations aim to optimally fit therapeutic regimes to patients and therefore reduce undesired side effects.

So far, the classification of subtypes and thus the therapeutic decisions are based on empirical impressions of the physician, predominantly underlined by motor scores such as the UPDRS[4] or the Hoehn and Yahr Scale[5]. In the last decades further knowledge about Parkinson's disease, especially with respect to non-motor symptoms[6], was gained.

Cluster analyses (CA)[7] have been extensively used to better identify PD subtypes in the motor and non-motor domain independently from the clinical expertise of the doctor (e.g. [8–12]). These methods comprise the detection of new subtypes based on pre-defined clinical characteristics such as age at onset, motor phenotype, non-motor symptoms or disease progression. However, all studies highly vary in the final number of characterized clusters, sample size, inclusion criteria as well as included variables, which limits comparability.

We considered, that beside motor and non-motor phenomena, some more basic features might seem to play a crucial role in the development of Parkinsonian symptoms. Hence, the following measures should be considered in treatment decisions for PD patients: (1) Gender differences: PD incidences in men with a prevalence of 1.5 times higher than in women[13]; additionally men show an earlier disease onset and have more diverse clinical profiles than women[14]. (2) Gene polymorphism: Likewise, D2 and D3 receptor polymorphism might be of great importance when delineating PD subtypes. An association of receptor polymorphisms - as disease causing variants - has been reported for Parkinson's disease[15,16]. An influence of these polymorphisms on medication response and occurrence of side effects in individual patients is part of ongoing research ([17–21]).

In order to proof our hypothesis of an influence of dopamine receptor polymorphisms and gender on the daily needed levodopa dosage (LED), we wanted to explore whether motor symptoms, the dopamine receptor polymorphism and further clinical demographic data can reveal new patient subtypes, which could lead to a better prediction of LED. We hence utilize a non-hierarchical clustering approach on our patient cohort and subsequently perform multiple linear regressions for each of the delineated clusters modeling the LED in each individual patient.

Methods

All patients with Parkinson's disease or the legally authorized representative of the patients gave written informed consent. Approval of the ethics commission of Cologne University's Faculty of Medicine (Nr.: 12–268) was obtained. The study was performed in accordance with the Declaration of Helsinki. Detailed patient information, methods and any associated references are available in the supplementary information of this paper.

Results

We performed k-means clustering for 91 patients with idiopathic PD (iPD) including D2 and D3 receptor polymorphisms, standardized medication response, the age at onset and symptom onset side, a score relating the tremor/ akinetic-rigidity score, disease progression in the OFF state and the patient's gender as input variables (cf. Table 1). After validating clustering results of 2 to 10 clusters, the optimal solution results in three distinct groups of patients (cf. Figure 1a). *Post-hoc* analyses of all input variables sorted by the allocated groups revealed significant differences in patient's gender ($p < 0.0001$), their individual standardized medication response ($p < 0.0001$), their D2 receptor polymorphism ($p < 0.0001$) and symptom onset side ($p = 0.016$). All other variables showed no significant group differences (cf. Supplementary Table S2).

Table 1
Patient demographics

Number of patients	**91**
Sex men/ women (% men)	62 (68 %)
Age at onset (yrs)	58 (± 10)
Symptom onset left (% left)	44 (48 %)
Disease progression ‘off’	5 (± 2)
Medication response	0.41 (± 0.2)
Tremor-/akinetic-rigid-score (T-/AR-score)	0.3 (± 0.5)
DRD2 positive (A/A or A/G)	27 (30 %)
DRD3 positive (C/C or C/T)	36 (40 %)
Variables included in CA. Mean (SD) in continuous variables; absolute numbers and percentage in dichotomous variables.	

In summary, the three clusters could be characterized mainly by gender and D2 receptor polymorphism. Whereas one cluster consisted of only men with D2 receptor negative genotype, another cluster included only women with mostly D2 receptor negative genotype. The third cluster mainly comprises male patients with D2 receptor positive genotype. Interestingly, also standardized medication response of the three identified clusters significantly differed, i.e., men without D2 risk alleles have a higher standardized medication response in comparison to the two other patient groups ($p < 0.0001$; cf. Figure 1b). Additionally, symptom onset side significantly differed between subgroups. In brief our findings are summarized in Table 2.

Table 2
Significant cluster characteristics.

	Cluster 1	**Cluster 2**	**Cluster 3**
gender	women only	men only	mostly men
symptom onset left	equal	less left	more left
disease progression	low	fast	low
standardized medication response	lower	high	lower
D2 receptor polymorphism	mainly negative	all negative	mainly positive
Overview of the significant cluster characteristics in words.			

Multiple linear regression model

The consecutive regression analysis revealed an optimal model for cluster 1 [including (i) symptom onset side; (ii) tremor-/akinetic-rigidity score, (iii) D2 receptor polymorphism, (iv) standardized medication response, (v) interaction of disease progression OFF and standardized medication response] to explain adjusted levodopa equivalent dosage (aLED) with a significant regression equation ($F(5,20) = 11.843$, $p < 0.0001$) and an adjusted $R^2 = 68\%$. Regression analysis of cluster 2 yielded in an optimal model [including (i) disease progression OFF, (ii) standardized medication response, (iii) interaction between disease progression OFF and standardized medication response] to predict LED ($F(3,30) = 3.854$, $p = 0.0019$) with an adjusted R^2 of 21%. For cluster 3 no significant regression model of aLED could be determined. However, the model explaining the highest amount of variation is based on a single variable (standardized medication response) with adjusted $R^2 = 8{,}4\%$ ($F(1,29) = 3.763$, $p = 0.062$).

Discussion

We demonstrate the feasibility of a clustering approach resulting in three distinct iPS patient subgroups. Extending earlier studies, describing motor and non-motor characteristics in their clustering approaches, we also considered parameters for (1) gender and (2) D2 gene polymorphism. The results of our analyses suggest, that these additional features might also have an impact on the development of Parkinson's disease affecting the treatment response to dopamine or dopamine equivalents.

An extensive body of literature exists on the association of gender and iPD (for review e.g. see Picillo et al., 2016[22]). A clear trend of a 1.5 times higher incidence of iPD in men is well described[14]; here the neuroprotective influence of estrogen, the genetically determined structural and functional cerebral differences as well as environmental factors are stated as putative mechanisms. Considering the fact that two out three clusters consisted only of men or women, gender seems to be a highly predictive factor in iPD and should be generally considered in the analysis of parkinsonian data.

As recently shown in Pelzer et al., 2019[23], D2 polymorphism seems to have a neuroprotective influence on neurons in the nigro-striatal and satellite systems for patients with Parkinson's disease. Besides, the current study emphasizes an impact of D2 polymorphism also on the treatment response to dopaminergic drugs: (1) We were able to predict the daily levodopa intake of the individual patients in cluster 1 with very high significance. (2) Our findings, especially in cluster 2, fit well to previous studies, describing a rapid-disease progression in patients with right-dominant symptom onset compared to those with left-sided symptom onset, as shown in a large scale prospective study[24]. These patients were all D2 negative.

An altered anatomical background in basal ganglia loops for right- or left-affected parkinsonian patients has already been confirmed in a recent support vector machine analysis[25]. In this study right-dominant

expression of iPD has been connected to faster disease progression[26], indicating a different degeneration pattern with altered neuronal firing rates in oscillatory networks. However, the role of the D2 receptor polymorphism in these different clinical situations is still unclear. Other studies investigating the association of iPD with the D2 genotype published contradictory findings. Whereas one study could show an increased risk of motor fluctuations[27], another study could not state any influence of D2 gene polymorphism on dyskinesia[28]. An effect of D2 polymorphism on structural brain connectivity has been shown in Pelzer et al., 2019[23] in patients with the wild type compared to the D2 risk type. This correlation of structural changes in brain connectivity due to D2 genotypes can further be linked to differences in the treatment response of individual genotypes. Hence, it might explain differences in the development of side effects like motor fluctuations in Parkinson's disease. Herewith these results indicate the relevance of the D2 receptor polymorphism for future studies investigating dopaminergic side effects.

In conclusion, we consider these results as a major step to further establish predictive clinical models of iPD. In contrast to previous studies identifying subtypes of Parkinson's disease[8,12], we ignored non-motor scales and only focused on the implementation of parameters usually assessed in clinical routine (like age, gender, symptom onset side, motor scales, levodopa dosage per day). However, these features **plus** information about D2 receptor polymorphism provide sufficient information for building adequate models to predict the daily dosage of levodopa necessary to elevate parkinsonian symptoms. Based on this information the medical treatment and levodopa dosage could be individually customized to relief parkinsonian symptoms more efficient while reducing potential side effects.

Declarations

Author contributions:

MT, CE and LT designed the research; SS, EAP and FS acquired data; CM, DLF and MS contributed analytic tools and analyzed the data; EAP and SS wrote the draft while MT and LT reviewed the manuscript.

Conflicts of interest:

LT received payments as a consultant for Medtronic Inc, Boston Scientific, SAPIENS, St. Jude Medical, Bayer Healthcare, UCB Schwarz Pharma, Archimedes Pharma. LT received honoraria as a speaker on symposia sponsored by TEVA Pharma, Lundbeck Pharma, Bracco, Gianni PR, Medas Pharma, UCB Schwarz Pharma, Desitin Pharma, Boehringer Ingelheim, GlaxoSmithKline, Eumecom, Orion Pharma, Medtronic, Boston Scientific, Cephalon, Abott, GE Medical, Archimedes, Bayer, TAD Pharma. EAP, SS DLF, CM, FS, MS, CE and MT had no conflicts of interest.

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Figures

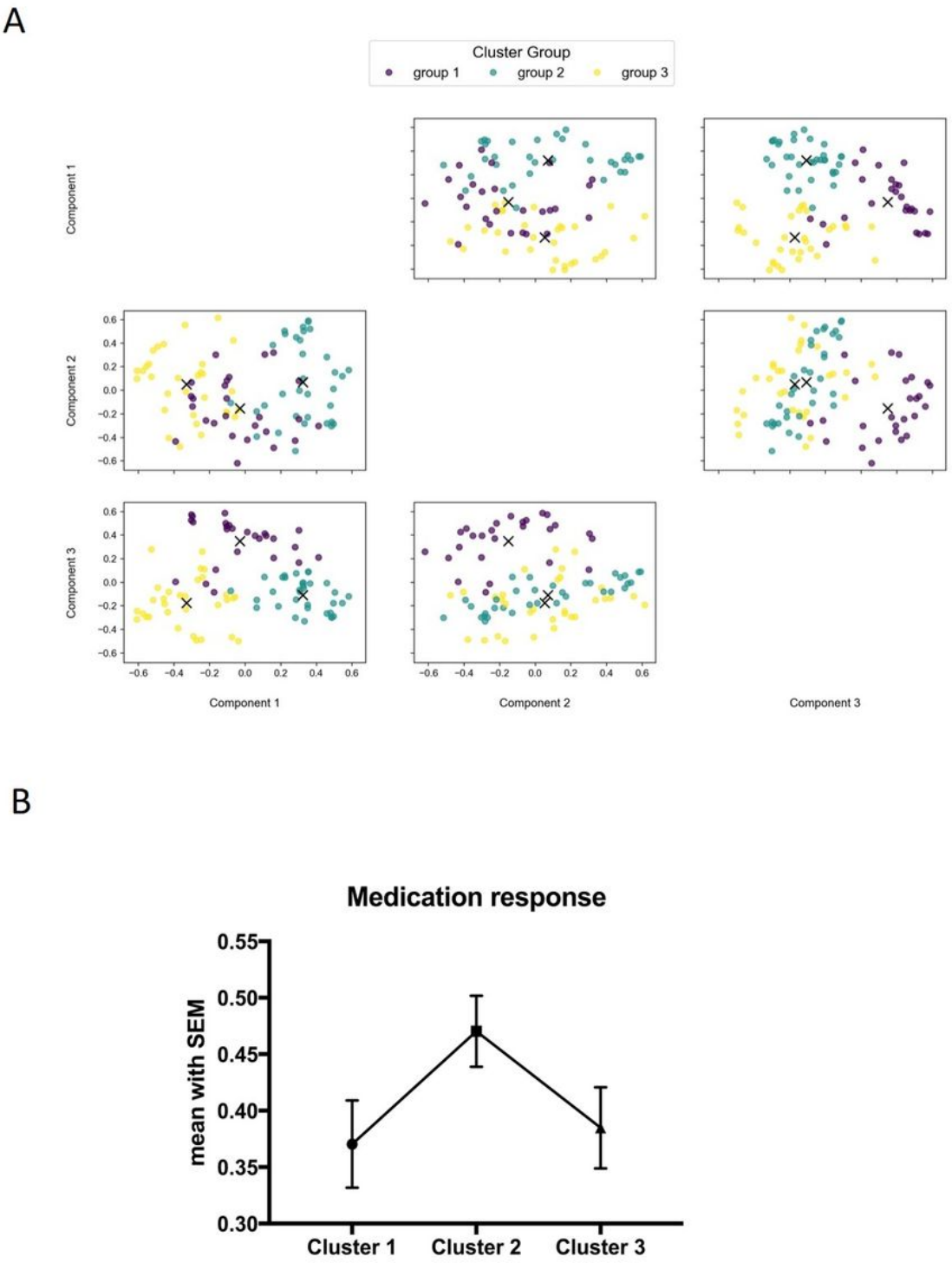

Figure 1

Overview of key results A: Results of k-means clustering with resulting three distinct groups (labeled in yellow, red and purple) exemplarily for the first three components (out of 8 components). B: Cluster 2 showed the best medication response with a significant difference to cluster 1 and 3. Differences are marked at significance level of $p < 0.0001$ (****).

Supplementary Files

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