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조기 파킨슨병 환자에서 군집분석에 의한 비운동성 증상의 아형 분류에 관한 연구

Identification of the subgroups of nonmotor symptoms in patients with early Parkinson's disease using cluster analysis

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양 희 준

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Abstract

Introduction: Parkinson's disease is a clinically and pathologically heterogeneous disorder. Classical classification and data-driven classification of Parkinson's disease subtypes were both analyzed primarily based on motor symptoms and little attention has been paid to the clustering of nonmotor symptoms.

Methods: Clinical data on demographic, motor and nonmotor features including the Korean version of sniffin' stick test results and the responses to the nonmotor symptoms screening questionnaire were collected from 56 Parkinson's disease patients with disease onset within three years. Nonmotor symptom subgroups were classified using unsupervised hierarchical cluster analysis. Multiscale bootstrap resampling was conducted to validate the confidence of the hierarchical clustering.

Results: Forty nine (87.5%) patients indicated hyposmia. Dream-enactment behavior was higher in patients with lower olfactory score which implies worse olfactory function. In whole Parkinson's disease patients, cluster analysis of nine nonmotor

symptoms gave three clusters of symptoms. Cluster analysis in *de novo* subjects revealed the two main clusters without a priori assumptions about the relatedness. The clustering stability was assessed by comparing the results of different methods of measuring similarity and different measures of intergroup distance. We obtain the same clustering results concluded that the group structure stable.

Conclusion: Unsupervised clustering using hierarchical approach suggests three nonmotor symptom clusters in whole subjects and two clusters in *de novo* Parkinson's disease patients. This study is the first report about the identification of subtypes in multiple nonmotor symptom constellations.

Keywords: Parkinson's disease, Nonmotor symptom, Cluster analysis

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Contents

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Introduction

Parkinson's disease (PD) is a clinically and pathologically heterogeneous disease.(1) This heterogeneity is thought to indicate different subtypes of PD and many studies have sought to elucidate them.(2,3)

Classically, patients are divided by their motor phenotype into tremor-dominant (TD) or postural instability and gait disturbance (PIGD) subgroups, or classified by onset age as juvenile, young, or late onset PD.(2) In recent years, cluster analysis has been introduced as an objective data-driven grouping method.(4,5) Several cluster analysis studies showed that the age of onset,(5-10) rate of disease progression,(6-11) and motor phenotype(7,10-12) are the major dimensions of PD subtype classification.

The classical and data-driven approaches have focused primarily on the motor symptoms of PD. Some of the nonmotor symptoms, such as depression(9) or cognitive decline(5,12) were associated with previous classifications based mainly on motor phenotypes. Although recent result from two independent European cohorts has shown that the severity of nonmotor symptoms as well as motor complications are important factors in the characterization of PD subtypes,(13) little attention has been paid to the clustering of nonmotor symptoms

themselves.(3)

We propose the existence of different clusters of nonmotor symptoms using unsupervised hierarchical cluster analysis (HCA). To our knowledge, this is the first investigation of subtypes based on nonmotor symptom constellations in early stage PD.

Methods

1. Subjects

Between July 2007 and January 2008, 119 consecutive patients with idiopathic PD who met the diagnostic criteria of the United Kingdom Brain Bank were referred to our movement disorder center and clinically followed up. At referral, 56 of these patients who were within 3 years of motor symptom onset underwent olfactory function testing using the Korean version of the sniffin' stick (KVSS) test, the first olfactory function test to use odorants familiar to Koreans,(14) and were interviewed utilizing a nonmotor symptoms screening questionnaire designed to assess the presence or absence of predefined nonmotor symptoms (insomnia, orthostatic dizziness, depression, excessive daytime sleepiness, urinary symptom, memory disturbance, and dream-enactment behavior) as part of the routine clinical evaluation of PD patients.

We retrospectively performed a systematic review of the

hospital electronic medical records to collect clinical data on current age, age at onset of PD, gender, Hoehn and Yahr (H-Y) stage, dopaminergic drugs in a levodopa-equivalent daily dose (LEDD, mg/day), presence of constipation and responses to the nonmotor symptoms screening questionnaire. Constipation was defined as having fewer than three bowel movements per week. Patients had to be followed for at least 1 year to be included. None of the *de novo* PD patients, a subset of the all PD samples, had previously taken antiparkinsonian medication. The protocol was approved by the Seoul National University Hospital Institutional Review Board (IRB).

2. Smell testing

The KVSS test is a modified version of the "Sniffin' Stick" test.(14,15) Its validity and reliability have been demonstrated in comparison with the Cross-cultural Smell Identification Test (CC-SIT).(16) KVSS I is a rapid screening test and KVSS II is a comprehensive test that involves three subsets: threshold, discrimination, and identification. The olfactory threshold was

defined as the mean concentration at which the pen containing *n*-butanol was differentiated correctly four times from two blank pens. Olfactory discrimination was assessed using triplets of odorant pens in which two pens have identical odors and the other has a different odor, and the patients identify the pen with a different odorant. For olfactory identification, all 16 different odorants familiar to Koreans (cinnamon, licorice, soy sauce, garlic, pine resin, leather, sesame oil, fish, coffee, rose, peppermint, orange, apple, banana, lemon, and pineapple) are presented in felt-tip pens, with the patients choosing one of four odor items.(17) The scores range between 0 and 16 in all three subsets. The sum of the threshold, discrimination, and identification subset scores is presented as the composite threshold-discrimination-identification (TDI) score.

3. Statistical analysis

Statistical analyses were performed with IBM SPSS statistics version 19.0 (IBM, Somers, NY) and the open-source statistical software R version 2.15.1 (http://www.r-

project.org). The chi-square test and Fisher's exact test were used to determine the relationship between olfactory dysfunction and other nonmotor symptoms. Either Student's t-test or Mann-Whitney U test was used to analyze clinical differences between the two olfactory groups. The results were considered statistically significant at $P < 0.05$. Unsupervised HCA was performed and the clustering results are shown using a dendrogram. The main advantage of an unsupervised hierarchical approach is that it can be applied when the optimum number of clusters is not known in advance.(18) We used Yule's Q as a measure of similarity for asymmetric binary variables. The dissimilarity between clusters was calculated by the most common method, unweighted pair groups method average (UPGMA) also known as between-group average method.(19) Different methods of measuring similarity (Yule's Q, Jaccard's coefficient, and Dice's coefficient) and different measures of intergroup distance (UPGMA, average linkage within-groups method) were used to demonstrate the stability of the clustering.(18,19) Multiscale bootstrap resampling was

performed with the R package *pvclust* version 1.2-2 to compute the confidence of the hierarchical clustering with 1000 bootstrapped samples.(20,21) Clusters with approximately unbiased probability value (AU *P* value) > 95% were considered significant.(20)

Results

Table 1 shows the demographic and clinical characteristics of the subjects. The 56 patients included 28 men and 28 women (age, 46–81 years). Twenty-seven patients were newly diagnosed *de novo* PD patients. No subject had motor fluctuation or levodopa-induced dyskinesia. The KVSS tests were well accepted by all patients. Forty-nine patients (87.5%) had hyposmia based on the reported criteria.(14,16)

The patients were divided into high- and low-scoring groups using the median TDI score. Gender distribution, mean current age, disease duration, LEDD, and H-Y stage did not differ between the two olfactory groups (Table 1). Dream-enactment behavior was greater in patients with lower TDI scores, which imply impaired olfactory function (P = 0.029 for all PD patients; P = 0.046 for *de novo* PD patients). There were no significant differences in other nonmotor symptoms (Figs. 1A and 1B).

For all of the PD patients, the cluster analysis of nine nonmotor symptoms gave three clusters of symptoms without a

priori assumptions about relatedness. Figure 2A shows the corresponding dendrogram based on UPGMA distance. Cluster 1 included three symptoms: hyposmia, dream-enactment behavior, and constipation. Cluster 2 comprised memory disturbance and orthostatic dizziness. Cluster 3 contained urinary symptoms and excessive daytime sleepiness.

HCA in the *de novo* PD group revealed the two main clusters (Fig. 2B). Cluster 1 was defined by hyposmia, dream-enactment behavior, and constipation. The larger cluster 2 was defined by depression, insomnia, memory disturbance, orthostatic dizziness, excessive daytime sleepiness, and urinary symptoms.

The clustering stability was assessed by comparing the results of different methods of measuring similarity and different measures of intergroup dissimilarity. We obtained the similar clustering results and concluded that the group structure was stable.

Table 1. Demographics and clinical profiles of the PD sample

Characteristics	All PD sample (n = 56)				*de novo* PD sample (n = 27)			
	Total	TDI top (n=28)	TDI bottom (n=28)	*P*	Total	TDI top (n=14)	TDI bottom (n=13)	*P*
Age, y	64.0 (8.5)	62.1 (9.9)	65.9 (6.5)	.101	64.5 (7.7)	64.4 (8.2)	64.7 (7.4)	.912
Gender (% male)	50.0	42.9	57.1	.285	48.1	42.9	53.8	.568
Age at PD onset, y	62.6 (8.8)	60.7 (10.5)	64.5 (6.4)	.103	63.6 (8.0)	63.4 (8.5)	63.7 (7.8)	.934
Duration on PD, y	1.6 (0.9)	1.5 (1.0)	1.6 (1.0)	.871	1.3 (0.8)	1.2 (0.7)	1.4 (0.9)	.450
Hoehn and Yahr stage	2.0 (0.7)	2.0 (0.7)	2.1 (0.7)	.772	2.1 (0.7)	2.1 (0.7)	2.0 (0.7)	.903
I (%)	16 (28.6)	8 (28.6)	8 (28.6)		6 (22.2)	3 (21.4)	3 (23.1)	
II (%)	30 (53.6)	15 (53.6)	15 (53.6)		16 (59.2)	8 (42.9)	8 (38.5)	
III (%)	10 (17.9)	5 (17.9)	5 (17.9)		5 (18.5)	3 (21.4)	2 (15.4)	

LEDD, mg/day	149.6 (231.1)	101.2 (188.1)	198.1 (261.8)	.118				
KVSS I	5.0 (1.5)	5.7 (0.7)	4.1 (1.4)	<0.001	5.3 (1.2)	5.9 (0.7)	.4.7 (1.3)	.004
KVSS II threshold	4.1 (3.5)	6.2 (3.3)	2.0 (2.1)	<0.001	4.6 (3.8)	7.1 (3.5)	1.8 (1.5)	<0.001
KVSS II discrimination	8.0 (2.6)	9.6 (1.9)	6.4 (2.3)	<0.001	8.3 (3.3)	9.9 (2.4)	6.6 (3.3)	<0.001
KVSS II identification	8.2 (2.7)	10.1 (2.2)	6.3 (1.6)	<0.001	8.7 (3.1)	10.7 (2.7)	6.6 (1.9)	.006
TDI score	20.1 (6.6)	25.5 (3.4)	14.7 (4.1)	<0.001	21.3 (7.4)	27.1 (2.4)	15.0 (5.6)	<0.001

Data are shown mean ± standard deviation unless otherwise indicated.

PD, Parkinson’s disease; LEDD, levodopa equivalent daily dose; KVSS, Korean version of the sniffin’ stick; TDI, threshold−discrimination−identification.

Figure 1. Group differences in nonmotor symptoms based on KVSS II TDI score. Dream-enactment behavior was significantly higher in patients with lower olfactory score which implies worse olfactory function ($^{*}P = 0.029$; $^{**}P = 0.046$, chi-square test or Fisher's e.xact test, as appropriate). (A) All PD sample. (B) *de novo* PD sample.

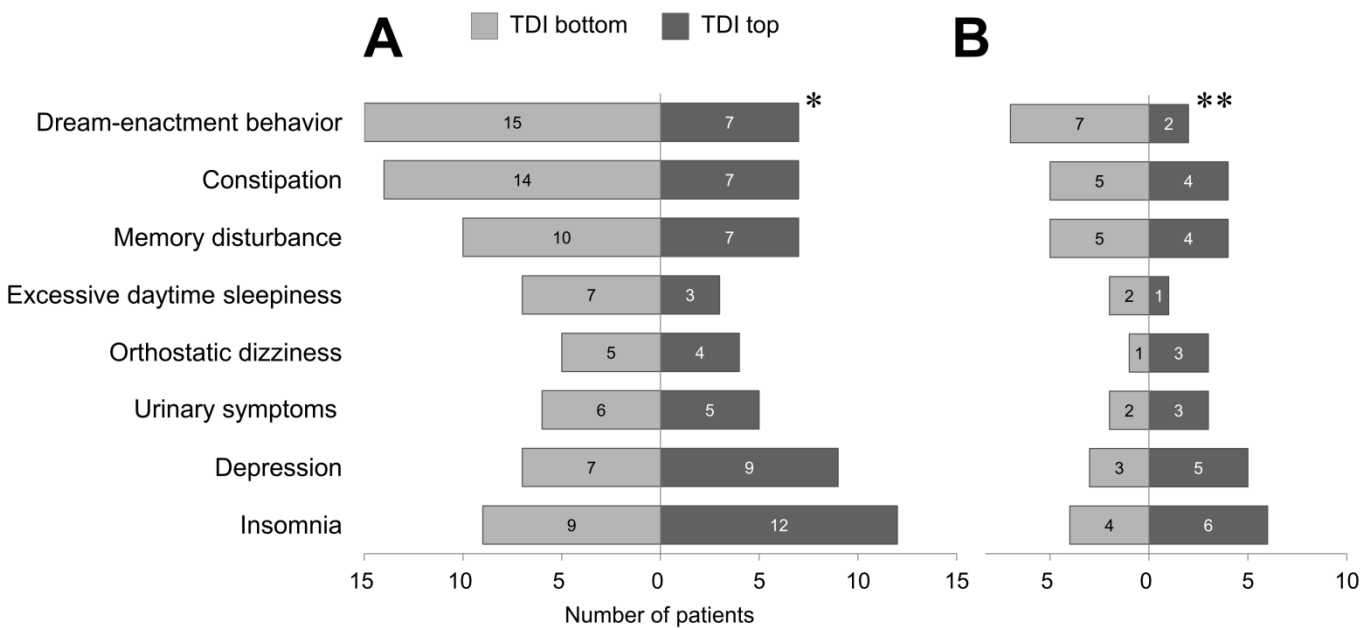
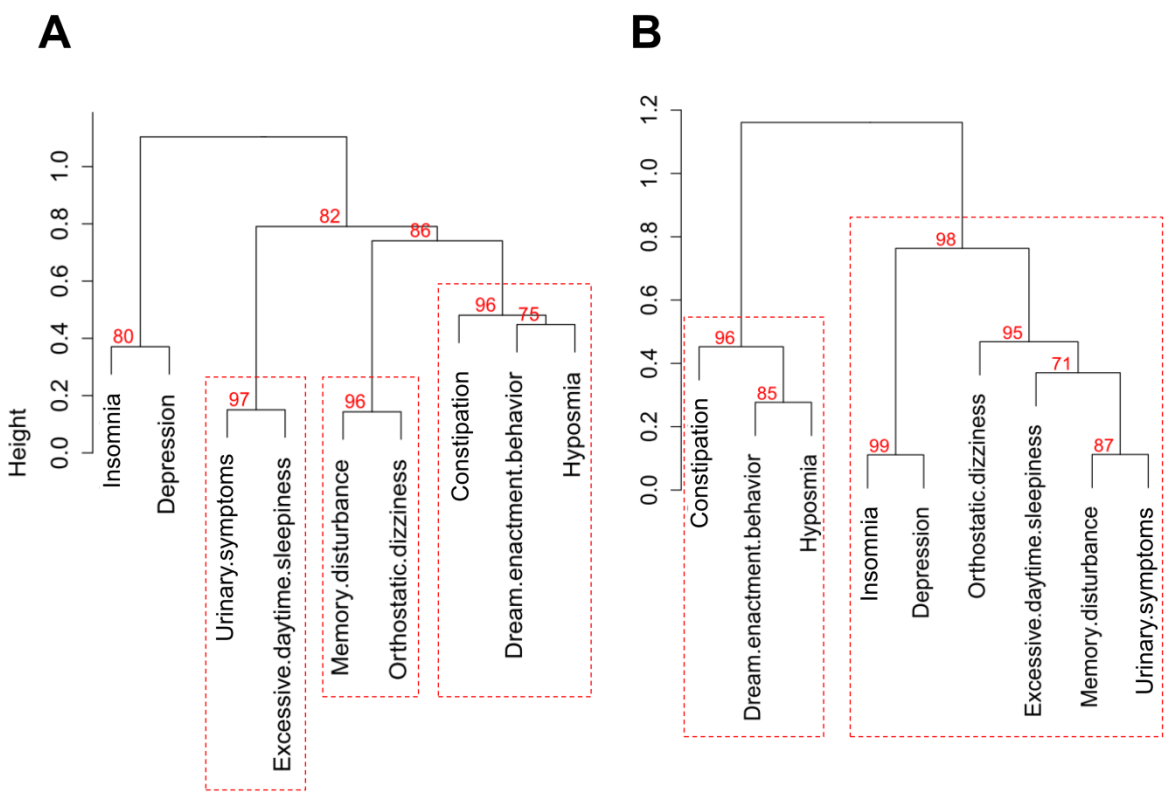


Figure 2. Dendrogram of hierarchical cluster analysis and multiscale bootstrap resampling results of nonmotor symptoms. The clusters with an approximately unbiased (AU, red) P−value >95% are highlighted by the dashed rectangles. (A) all PD patients. (B) *de novo* PD patients.



Discussion

In this study, 87.5% of patients were hyposmic as assessed by the KVSS olfactory test, which was in line with results from previous olfactory function studies in PD patients.(22,23)

Unsupervised cluster analysis suggests three nonmotor symptom clusters for the entire group of PD patients and two clusters for the *de novo* PD patients. This clustering result is in agreement with previous works demonstrating close relationships between olfactory dysfunction and rapid eye movement (REM) sleep behavior disorders.(24,25) Notably, our study suggests that depression is independent of olfactory dysfunction. This is a somewhat striking result, because depression, together with hyposmia, is a well-known predated nonmotor symptom.(26,27) Our result concurs with several studies showing that olfactory dysfunction did not correlate with depression.(28,29) The discrepancy with the findings of Berendse *et al.*, which addressed a potential correlation of hyposmia with depression, might partly depend on disease

duration or different olfactory function tests.(30)

While this cluster analysis gave interesting results, the clinical relevance of the complicated relationships among nonmotor symptoms is yet to be determined. A nonmotor symptom could be caused by coexisting conditions, e.g., daytime sleepiness due to nocturia. It is also possible that some symptoms are caused by PD medication, such as levodopa or dopamine agonists.(31) In addition, the patterning of nonmotor symptoms seen in our results implicates common neuropathological and neurochemical processes underlying PD.(1,32,33) The non-dopaminergic pathway has been proposed as a shared mechanism for various nonmotor symptoms.(34,35)

One limitation of this study is the use of the nonmotor symptom questionnaire that has not been validated. Another limitation is its retrospective design, which potentially influences the generalizability of our results. Although we used multiscale bootstrap resampling to validate the confidence in the clusters, a larger study should be conducted to verify our

result.

This preliminary analysis examining the presentation of multiple nonmotor features suggests that it is possible to identify subgroups based on profiles of nonmotor symptoms. Future data-driven replications with larger independent populations are required, and these will increase our understanding of associations between various nonmotor symptoms in PD patients.

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초 록 (국문)

서론: 파킨슨병은 임상적으로 또는 병리적으로 이질적인 질환들의 집합체로 이해된다. 그러나 파킨슨병의 기존 분류들은 고전적인 분류법 및 새로운 자료 주도적 분류법 모두 기본적으로 파킨슨병의 운동증상에 기초하여 전개되었으며, 비운동성 증상에 의한 파킨슨병의 분류에 대해서는 연구가 아직 이루어진 바가 없다.

방법: 본 연구는 증상 발생 3년 이내의 영국 파킨슨병 학회 뇌은행의 기준에 따른 조기 파킨슨병 환자 56명을 대상으로 하여 한국형 후각검사 KVSS 검사 결과 및 비운동성 증상에 대한 구조화된 설문지를 이용한 면담과 의무기록을 토대로 자료수집을 시행하였으며, 조사된 비운동성 증상들에 대하여 비지도 위계적 군집 분석을 수행하였다.

결과: KVSS 검사 상 49명의 환자 (87.5%) 에서 후각 기능 저하를 보였으며, 후각 기능이 저하된 집단에서 보다 높은 '꿈의 행동화' 빈도를 보였다 (모든 환자의 경우 P = 0.029; 항파킨슨 약물을 복용하지 않은 환자의 경우 P = 0.046). 군집분석 결과 모든 파킨슨병 환자의 경우 비운동성 증상의 유무에 따라 3개의 군집으로 구분되었으며 항파킨슨 약물을 복용하지 않은 환자에서는 2개의 군집으로 구분되었다.

결론: 본 연구는 다양한 비운동성 증상의 유무에 기반하여 군집 분석의 방법론에 의해 파킨슨병을 분류한 최초의 연구이다.

주요어: 파킨슨병, 비운동성 증상, 군집분석

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