Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.zju.edu.cn/jzus; www.springerlink.com
E-mail: jzus@zju.edu.cn

Clinical heterogeneity in patients with early-stage Parkinson's disease: a cluster analysis*

Ping LIU[1], Tao FENG[†‡1], Yong-jun WANG[1], Xuan ZHANG[1], Biao CHEN[2]

([1]*Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, China*)

([2]*Department of Neurology, Beijing Xuanwu Hospital, Capital Medical University, Beijing 100053, China*)

[†]E-mail: happyft@sina.com

Received Mar. 7, 2011; Revision accepted May 26, 2011; Crosschecked Aug. 4, 2011

Abstract: The aim of this study was to investigate the clinical heterogeneity of Parkinson's disease (PD) among a cohort of Chinese patients in early stages. Clinical data on demographics, motor variables, motor phenotypes, disease progression, global cognitive function, depression, apathy, sleep quality, constipation, fatigue, and L-dopa complications were collected from 138 Chinese PD subjects in early stages (Hoehn and Yahr stages 1–3). The PD subject subtypes were classified using *k*-means cluster analysis according to the clinical data from five- to three-cluster consecutively. Kappa statistical analysis was performed to evaluate the consistency among different subtype solutions. The cluster analysis indicated four main subtypes: the non-tremor dominant subtype (NTD, *n*=28, 20.3%), rapid disease progression subtype (RDP, *n*=7, 5.1%), young-onset subtype (YO, *n*=50, 36.2%), and tremor dominant subtype (TD, *n*=53, 38.4%). Overall, 78.3% (108/138) of subjects were always classified between the same three groups (52 always in TD, 7 in RDP, and 49 in NTD), and 98.6% (136/138) between five- and four-cluster solutions. However, subjects classified as NTD in the four-cluster analysis were dispersed into different subtypes in the three-cluster analysis, with low concordance between four- and three-cluster solutions (kappa value=−0.139, *P*=0.001). This study defines clinical heterogeneity of PD patients in early stages using a data-driven approach. The subtypes generated by the four-cluster solution appear to exhibit ideal internal cohesion and external isolation.

Key words: Parkinson's disease, Heterogeneity, Subtype, Cluster analysis
doi:10.1631/jzus.B1100069 **Document code:** A **CLC number:** R741

1 Introduction

The clinical variability among patients with Parkinson's disease (PD) suggests a relatively high level of heterogeneity in the disease. Identifying PD subtypes is important for understanding the mechanisms of disease and developing appropriate treatment strategies (van Rooden *et al*., 2010). A number of PD subtypes have been recognized (Hoehn and Yahr, 1967; Zetusky *et al*., 1985; Golbe, 1993; Graham and Sagar, 1999; Lewis *et al*., 2005; Reijnders *et al*., 2009). Using the motor symptoms present at time of diagnosis, there are "hypokinetic-rigid", "tremor-dominant", and "postural instability-gait disorder" forms (Zetusky *et al*., 1985). Based on the age of disease onset, juvenile onset, young onset, and late onset cases have been distinguished (Golbe, 1993). Several studies have used cluster analysis of clinical data to segregate patients into subtypes. Using this technique, Graham and Sagar (1999) divided patients into "motor only", "motor and cognitive", and "rapidly progressive" subtypes. Lewis *et al*. (2005) concentrated on the early phase of the disease and favored four subgroups: younger disease onset (YO), tremor dominant (TD), non-tremor dominant (NTD) with cognitive impairment, and rapid motor progression without cognitive impairment. In a

‡ Corresponding author

* Project (No. 2006AA02A408) supported by the National High-Tech R & D Program (863) of China

separate cohort, using different variables, Reijnders *et al.* (2009) effectively identified the similar four subgroups that were identified by Lewis *et al*. (2005).

The majority of initial attempts to classify PD clinically were based on prospective assumptions (Foltynie *et al*., 2002; van Rooden *et al*., 2010). This general method suffers from the arbitrariness of the choice of initial subtype. Further, the discrepancies in the choice of clinical variables, inclusion criteria, assessment techniques, and subjects limit the comparability of results between studies (van Rooden *et al*., 2010). Cluster analysis has been used in several studies to identify the heterogeneity of PD (Graham and Sagar, 1999; Lewis *et al*., 2005; Post *et al*., 2008; Reijnders *et al*., 2009). This method is considered useful and objective, but should be used with care and awareness that the choice of variables selected for inclusion in a cluster analysis and the number of clusters sought can have profound effects on the results (Everitt *et al*., 2001).

In previous studies, variables selected in the cluster analysis have not been sufficiently comprehensive. Numerous studies have indicated that non-motor symptoms (NMSs) are an integral symptom complex of PD. Constipation, depression, fatigue, and sleep dysfunction are particularly likely to predate motor signs (Chaudhuri *et al*., 2006; Chaudhuri and Naidu, 2008). Some NMSs, such as depression, cognitive impairment, and psychopathology, have been used as variables for classifying PD phenotypes (Lewis *et al*., 2005; Post *et al*., 2008; Reijnders *et al*., 2009). However, other NMSs that may predate the motor signs (especially constipation, fatigue, and sleep dysfunction) have generally been overlooked. The rate of disease progression itself has been considered as a basis for sub-classification, and most studies have evaluated the progression of disability using the Hoehn-Yahr (H-Y) stages (Hoehn and Yahr, 1967; Foltynie *et al*., 2002). In the clinicopathological study of PD subtypes by Selikhova *et al*. (2009), onset time of clinical features was highlighted without considering the severity of symptoms. Except the study of Lewis *et al*. (2005), the classification consistency between different cluster solutions using a data-driven approach has rarely been investigated.

A more rigorous study design with respect to the included variables, data processing, and cluster analysis may advance knowledge regarding the heterogeneity of PD. In the present study, we specifically aimed to classify different subtypes in Chinese patients with early-stage PD (H-Y stages 1–3) using *k*-means cluster analysis with a more comprehensive range of variables. The variables introduced in the present data-driven approach were all determined on the basis of standardized data collection with rating scales. A kappa test was then used to assess classification consistency between different cluster solutions, as well as between the cluster analysis and the classification according to motor phenotype.

2 Subjects and methods

2.1 Subjects

The study population comprised outpatients diagnosed with idiopathic PD of H-Y stages 1–3 admitted to Beijing Tiantan Hospital between April 2008 and July 2009. All subjects satisfied the United Kingdom Brain Bank Criteria for PD (Gibb and Lees, 1988). Participants were excluded if they required an assistive device for ambulation and exhibited an atypical parkinsonian syndrome or a primary initial diagnosis of dementia. No participant exhibited evidence of psychosis, neuroleptic use, epilepsy, stroke, unstable cardiovascular disease, or other uncontrolled chronic conditions that may have interfered with either the conduct of the testing protocol or interpretation of the results. Participants were assessed by neurologists experienced in examining PD patients. The same researcher administered all assessments when the participants' antiparkinsonian medications were working ('on' state).

All procedures were conducted in accordance with ethical standards of the Helsinki Declaration. Permission for the study was obtained from the local research ethics committee, and written informed consent was obtained from all participants.

2.2 Clinical evaluation

2.2.1 Demographics data

Details of gender, age, age at disease onset, disease duration, education level, medication history,

and current medications and dosage were collected carefully by face-to-face interview. The H-Y scale was used for disease staging.

2.2.2 Motor symptoms

Objective motor symptoms were assessed using the motor section of the unified Parkinson's disease rating scale (UPDRS III) (Fahn *et al*., 1987). UPDRS items 20 (tremor at rest) and 21 (action or postural tremor of hands) are for the motor section tremor score, 22 (neck and limbs rigidity) for the motor section rigidity score, 23 (finger movements), 24 (hand movements), 25 (rapid alternating movements of hands), 26 (leg agility), and 31 (body bradykinesia and hypokinesia) for the motor section hypokinesia score, and 27 (arising from a chair), 28 (posture), 29 (gait), and 30 (postural stability) for the postural instability/gait disorder (PIGD) score (Williams *et al*., 2007). The total tremor score was derived from the mean of items 16 and 20–21 on the UPDRS (total score divided by 8, the number of items included) and represented the degree of tremor reported in the activity of daily living (ADL) section of the UPDRS, along with the objective tremor at rest and during action, as determined by a physical examination. The total non-tremor score was calculated by dividing the sum of items 5, 7, 12–15, 18, 19, and 22–31 on the UPDRS by 26. This measure assessed speech, swallowing, ability to turn in bed, falls, freezing, and walking from the ADL section as well as speech, facial expression, rigidity, bradykinesia, ability to stand, posture, gait, and postural stability determined by the motor examination in the UPDRS (Lewis *et al*., 2003). The motor phenotype was assessed by the ratio of total tremor to non-tremor score (Lewis *et al*., 2003).

2.2.3 Rate of disease progression

Total disease progression was determined from the UPDRS total score of parts I–III/disease duration (Lewis *et al*., 2005), UPDRS III score/disease duration for motor disorder progression rate, and UPDRS II score/disease duration for ADL progression rate (Reijnders *et al*., 2009). This measure allows the comparison of the rate of disease progression between subjects with different disease durations assessed at a single time point.

2.2.4 Non-motor symptoms

Global cognitive function: The mini-mental state examination (MMSE), with scores ranging from 0–30, was used to assess global cognitive impairment (Folstein *et al*., 1975). The raw score needs to be corrected for educational attainment (Li *et al*., 1988). Depression: Presence and severity of depressive symptoms were determined using the 24-item Hamilton (1960) rating scale for depression (HAMD-24). Depressive symptoms were categorized as none (HAMD scores <8), possible (8–20), definite (21–35), and severe (>35). Sleep quality: The Pittsburgh sleep quality index (PSQI) was used to assess sleep quality and disturbances (Smyth, 2003). Sleep disorders were defined by a score of ≥8 on the PSQI. Apathy: UPDRS part I item 4 was used to determine apathy score (Reijnders *et al*., 2009). Constipation: Constipation was diagnosed according to the Rome diagnostic criteria for the functional constipation (Thompson *et al*., 1999). Fatigue: The presence and severity of fatigue were assessed using the fatigue severity scale (FSS). Fatigue was considered to be present if subjects scored ≥36 on the FSS (Krupp *et al*., 1989).

2.2.5 Quality of life

Subjects' quality of life was measured using the total score in part II of the UPDRS (Reijnders *et al*., 2009).

2.2.6 L-dopa complications

L-dopa complications were assessed with the UPDRS part IV score (Reijnders *et al*., 2009).

2.3 Derivation of variables used in the cluster analysis

The clinical feature variables used in the cluster analysis are showed in Table 1.

2.4 Classification based on motor phenotype

The subjects were divided into three subtypes on the basis of their motor phenotypes, which included the PIGD, TD, and indeterminate subtypes, following the criteria used in previous studies (Jankovic *et al*., 1990; Lewis *et al*., 2003). The PIGD subtype was defined as subjects with the ratio of total tremor

Table 1 Derivation of variables used in the cluster analysis

Parameter	Clinical variables
Demographics data	
Age	Age
Age at disease onset	Age at disease onset
Disease duration	Disease duration
Disease staging	Hoehn-Yahr stage
Motor variables	
Tremor	Mean score of UPDRS items 20, 21
Rigidity	Mean score of UPDRS item 22
Hypokinesia	Mean score of UPDRS items 23, 24, 25, 26, 31
PIGD	Mean score of UPDRS items 27, 28, 29, 30
Motor phenotype	Ratio of total tremor to non-tremor score
Non-motor variables	
Global cognitive function	MMSE total score
Depression	HAMD total score
Sleep disorders	PSQI total score
Constipation	Constipation (1=yes, 0=no)
Fatigue	FSS scale score
Disease progression	
Total disease progression rate	UPDRS total score parts I, II, III/ disease duration
Motor disorder progression rate	UPDRS total score part III/disease duration
ADL progression rate	UPDRS total score part II/disease duration
L-dopa complications	UPDRS total score part IV

score to total PIGD score equal to or less than 1.0, whereas subjects with a ratio of 1.5 or more were defined as TD subtype. Subjects were classified as indeterminate subtype if they exhibited a tremor/ PIGD ratio between 1.0 and 1.5.

2.5 Statistical analysis

K-means cluster analysis was performed on the subjects with the five-, four-, and three-cluster solutions, using the standardized scores of the clinical variables (Table 1) to indentify the clinical heterogeneity of subjects with early-stage PD. One-way analysis of variance (ANOVA), cross-tabulation analysis, and Kruskal-Wallis test were conducted to compare the general characteristics of the subjects. Pair-wise comparisons were made using chi-square test for categorical variables and two-tailed *t*-test or the Mann-Whitney *U*-test, as appropriate, for continuous variables. Kappa statistical analyses were performed to evaluate the classification consistency between subtype systems based on cluster analysis and motor phenotype, as well as between four- and three-cluster analysis subtype solutions. All reported test results were two-tailed and a P value <0.05 was considered significant. Analyses were performed with SPSS version 11.5.

3 Results

3.1 Demographic and clinical characteristics

We examined a total of 138 subjects with early-stage PD (H-Y: 1–3). The subjects included 58 females and 80 males, ranging in age from 30 to 81 years (mean±standard deviation (SD): (57.47±10.58) years). The mean age of disease onset was (53.57± 11.31) years, and the median disease duration was 3.0 years (range: 0.5–35.0 years). Of the subjects, 39 (28.3%) were in H-Y stage 1, 16 (11.6%) were in stage 1.5, 38 (27.5%) were in stage 2, 21 (15.2%) were in stage 2.5, and 24 (17.4%) were in stage 3.

3.1.1 UPDRS score

The mean UPDRS I–III score was 33.67±16.27, UPDRS II score was 10.30±5.09, and UPDRS III score was 21.11±11.49. According to UPDRS part I item 4, the median apathy score was 0.50 (range: 0–3).

3.1.2 HAMD score

More than half of the subjects (55.1%) scored ≥8 on the HAMD scale, with 45.7% exhibiting possible depression and 9.4% indicating definite depression. No subjects exhibited severe depression.

3.1.3 MMSE score

The mean MMSE score was 27.17±2.79. The global cognitive function of 137 subjects was normal after being corrected by educational level, with only one subject exhibiting global cognitive impairment.

3.1.4 PSQI score

The mean PSQI score was 6.23±3.84. Forty-one (29.7%) subjects exhibited sleep disorders following the criteria with PSQI score ≥8.

3.1.5 Fatigue

According to the FSS score, 68 (49.3%) subjects were defined as fatigued. The mean FSS score of these subjects was 51.24±8.27.

3.1.6 Constipation

Almost half of the subjects (48.6%) exhibited constipation, according to the Rome diagnostic criteria for functional constipation.

3.2 Explorative cluster analysis

3.2.1 Five-cluster analysis

Five-, four-, and three-cluster analyses were consecutively conducted on the basis of standardized data collection. When a five-cluster analysis was applied, cluster 5 contained only a single subject. This subject exhibited an age of disease onset of 22 years, disease duration of 35 years, and H-Y stage of 2, but had a negative family history of neurodegeneration disease. The remaining four clusters were manifested as follows: (1) Cluster 1 (n=28): UPDRS rigidity (1.46±0.92), hypokinesia (1.16±0.77), and PIGD (1.05±0.74) scores were the highest among the five clusters, with a relatively mild depression (13.25±9.09). The rates of total disease, motor and ADL progressions were 26.83±6.81, 16.84±4.56, and 8.01±2.83, respectively. (2) Cluster 2 (n=7): the rates of disease progression, including total disease (55.43±7.98), motor (36.57±7.89), and ADL (15.57±4.16) progressions, were the fastest of the five clusters, with the latest age of disease onset ((61.57±6.90) years). The UPDRS rigidity (1.09±0.64), hypokinesia (1.14±0.55), and PIGD (0.96±0.30) scores were all second only to the cluster 1. The UPDRS part IV score was zero, and the UPDRS tremor score (median 0.20, range 0.00–0.57) was the lowest among the five clusters. (3) Cluster 3 (n=50): the mean age of disease onset in this cluster was (42.2±6.45) years, with relatively low PIGD (0.37±0.05) and hypokinesia (0.79±0.50) scores, slow disease progression, few L-dopa complications (median 1.20, range 0.00–9.00), and the lowest H-Y stage (1.75±0.69) of any cluster. (4) Cluster 4 (n=52): the ratio of tremor score to non-tremor score (1.16±0.77) was the highest among the five clusters, without apathy, global cognitive impairment, or motor complications.

Some variables were significantly different among the five clusters, including age at disease onset (F=65.503, P=0.000), UPDRS rigidity (F=3.541, P=0.009), PIGD score (F=4.106, P=0.003), ratio of tremor score to non-tremor score (F=4.854, P=0.000), falls score (F=3.054, P=0.009), total disease progression (F=178.443, P=0.000), motor disorder progression (F=155.698, P=0.000), ADL progression rate (F=84.871, P=0.000), and L-dopa complications (F=9.944, P=0.041). However, no significant differences were found in UPDRS tremor score, H-Y stage, HAMD score, MMSE score, constipation, or PSQI score.

3.2.2 Four-cluster analysis

When four-cluster analysis was applied, 28 subjects (20.3%) were classified as NTD, 7 (5.1%) as rapid disease progression subtype (RDP), 50 (36.2%) as YO, and 53 (38.4%) as TD. Comparisons of clinical features are shown in Tables 2 and 3.

3.2.3 Three-cluster analysis

The three-cluster analysis indentified the following subtypes: (1) YO (n=53, 38.4%): the mean age of disease onset was (42.0±6.96) years, with the lowest H-Y stage (1.78±0.69), PIGD score (0.66±0.37), and hypokinesia score (0.78±0.51), slowest disease progression; (2) TD (n=64, 46.4%): the ratio of UPDRS tremor to non-tremor score (1.06±0.96) was the highest in three subtypes; (3) RDP (n=21, 15.2%): the total (40.16±12.31), motor disorder (25.67±9.55), and ADL progression (11.54±4.35) rates were the rapidest, with the highest rigidity (1.30±0.79), hypokinesia (1.11±0.68), PIGD (1.11±0.66) scores, and H-Y stage (2.07±0.75).

3.2.4 Concordance between different cluster solutions

The majority of subject classifications (98.6%, 136/138) exhibited consistency in terms of subgroups between the five- and four-cluster solutions, 79.0% (109/138) between the four- and three-cluster solutions, and with a same percentage between the five- and three-cluster solutions. Overall, 78.3% (108/138) subjects were always classified between the same three groups (52 always in TD, 7 in RDP, and 49 in NTD) (Fig. 1). Kappa statistical analysis indicated poor consistency between the four- and three-cluster analyses (kappa value=−0.139, P=0.001).

Table 2 Group characteristics for the four-cluster solution

Parameter	Value				*P*-value
	NTD (*n*=28)	RDP (*n*=7)	TD (*n*=53)	YO (*n*=50)	
Age[a] (year)	61.57 (9.05)	62.21 (6.77)	64.77 (6.11)	46.76 (5.94)	<0.01
Age at disease onset[a] (year)	59.86 (8.66)	61.57 (6.90)	60.49 (5.60)	41.60 (6.90)	<0.01
Hoehn-Yahr stage[a]	2.07 (0.75)	2.00 (0.96)	1.94 (0.70)	1.77 (0.68)	0.321
Disease duration[b] (year)	1.25 (0.5–5.0)	0.50 (0.5–1.0)	4.00 (1.0–7.0)	3.75 (1.0–35.0)	<0.01
Mean UPDRS III tremor score[a]	0.40 (0.36)	0.20 (1.99)	0.43 (0.30)	0.41 (0.48)	0.551
Mean UPDRS III rigidity score[a]	1.45 (0.92)	1.09 (0.64)	0.79 (0.81)	1.00 (0.72)	<0.01
Mean UPDRS III hypokinesia score[a]	1.16 (0.76)	1.14 (0.55)	0.85 (0.70)	0.79 (0.50)	0.067
Mean UPDRS III PIGD score[a]	1.05 (0.74)	0.96 (0.30)	0.69 (0.37)	0.64 (0.37)	<0.01
Tremor/non-tremor score[a]	0.55 (0.52)	0.36 (0.32)	1.16 (0.99)	0.78 (0.63)	<0.01
UPDRS I+II+III/disease duration[a]	26.84 (6.81)	55.43 (7.98)	7.93 (3.77)	9.02 (5.36)	<0.01
UPDRS III/disease duration[a]	16.84 (4.56)	36.57 (7.89)	4.82 (2.64)	5. 59 (3.39)	<0.01
UPDRS II/disease duration[a]	8.01 (2.83)	15.57 (4.16)	2.54 (1.33)	2.85 (2.03)	<0.01
HAMD score[a]	13.25 (9.09)	10.43 (5.00)	8.47 (6.99)	9.54 (6.62)	0.047
MMSE score[a]	26.79 (3.95)	26.43 (2.76)	27.02 (2.66)	27.64 (2.07)	0.460
Apathy score[b]	1 (0–3)	1 (0–1)	0 (0–3)	1 (0–3)	0.388
PSQI score[a]	6.25 (4.24)	8.28 (3.68)	6.11 (3.67)	6.06 (3.82)	0.545
Sleep disorders[c]	8 (28.6%)	3 (42.9%)	15 (28.3%)	15 (30.0%)	0.982
FSS score[a]	31.50 (27.27)	27.14 (27.03)	23.17 (24.97)	31.66 (23.37)	0.311
Fatigue[c]	15 (53.6%)	3 (42.9%)	21 (39.6%)	29 (58.0%)	0.282
Constipation[c]	16 (57.1%)	2 (28.6%)	31 (58.5%)	18 (36.0%)	0.066
UPDRS IV score[a]	0.36 (1.06)	0.00 (0.00)	0.96 (1.74)	1.28 (2.08)	0.072

Data are shown as mean (SD)[a] for continuous variables with normal distribution, median (range)[b] for non-normal distribution variables, and *n* (%)[c] for categorical variables. ANOVA, cross-tabulation analysis, and Kruskal-Wallis test were conducted to compare the general characteristics of the subjects

Table 3 Pair-wise comparisons between the subtypes in the four-cluster solution

Parameter	*P*-value					
	NTD-RDP	NTD-TD	NTD-YO	RDP-TD	RDP-YO	TD-YO
Age (year)	NS	NS	<0.001	NS	NS	<0.001
Age at disease onset (year)	NS	NS	<0.001	NS	<0.001	<0.001
Disease duration (years)	<0.001	<0.001	<0.001	<0.001	0.037	NS
Mean UPDRS III rigidity score	NS	0.001	0.016	NS	NS	NS
Mean UPDRS III hypokinesia score	NS	NS	0.028	NS	NS	NS
Mean UPDRS III PIGD score	NS	0.019	0.010	NS	0.033	NS
Tremor/non-tremor score	NS	0.001	NS	<0.001	NS	0.022
UPDRS I+II+III/disease duration	<0.001	<0.001	<0.001	<0.001	<0.001	NS
UPDRS III/disease duration	<0.001	<0.001	<0.001	<0.001	<0.001	NS
UPDRS II/disease duration	<0.001	<0.001	<0.001	<0.001	<0.001	NS
HAMD score	NS	0.010	0.042	NS	NS	NS

NS: non-significant difference

3.3 Classification consistency between motor phenotypes and cluster analysis

In the motor phenotype classification, 84 subjects (60.9%) were classified as PIGD, 38 (27.5%) as TD, and 16 (11.6%) as indeterminate subtype. Subjects manifesting the same motor phenotype were dispersed into different subtypes in the cluster analysis (Fig. 2). The subtype systems of four- or three-cluster analysis were in poor consistency with the subtype system based on motor phenotype (kappa value=0.043, *P*=0.474; kappa value=−0.080, *P*=0.059, respectively).

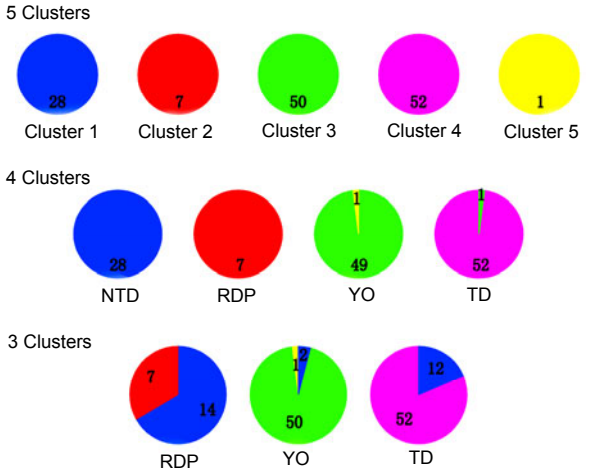

Fig. 1 PD subtypes in the successive cluster analyses
The diagram shows the classification of the subject subgroups derived in the five-, four-, and three-cluster solutions. The subjects included in cluster 1 (non-tremor dominant subtype (NTD)) and cluster 2 (rapid disease progression subtype (RDP)) in the five-cluster analysis belonged to the same subtypes independently in the four-cluster analysis. The separate one subject and the 49 subjects in cluster 3 (n=50, young-onset subtype (YO)) in the five-cluster analysis were classified into the same group in the four-cluster analysis independently. All subjects of the cluster 4 (tremor dominant subtype (TD)) and one subject of the cluster 3 in the five-cluster analysis were classified into one group in the four-cluster analysis. Twenty-eight subjects of NTD subtype in the four-cluster solution were dispersed into three groups in the three-cluster solution, with 12 (42.9%) segregated into the TD subtype, 14 (50.0%) into the RDP subtype, and 2 (7.1%) into the YO subtype

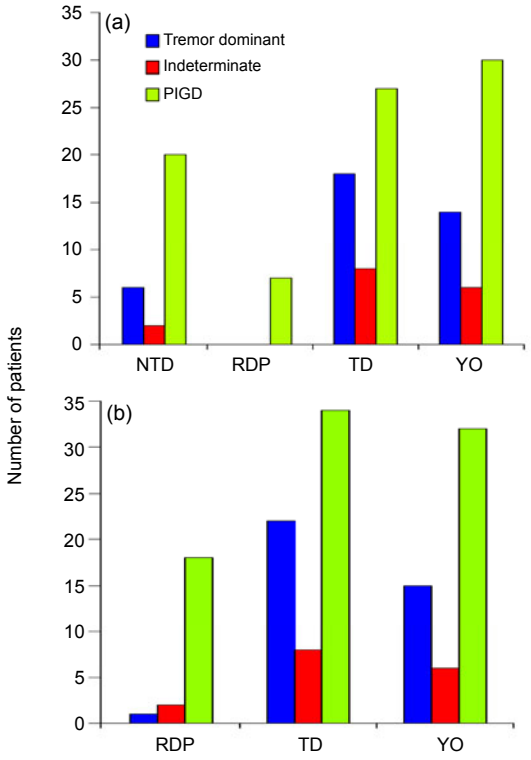

Fig. 2 Clinical motor phenotypes by four- and three-cluster subtypes
Subjects manifesting the same motor phenotype were dispersed into four-cluster (a) and three-cluster (b) analyses. NTD: non-tremor dominant subtype; RDP: rapid disease progression subtype; TD: tremor dominant subtype; YO: young-onset subtype; PIGD: postural instability/gait disorder

4 Discussion

The present study explored and confirmed the existence of distinct subtypes among Chinese PD patients in early stages using cluster analysis with a comprehensive range of variables. The four-cluster analysis demonstrated four main subtypes: the NTD, RDP, YO, and TD subtypes. The three-cluster analysis identified YO, TD, and RDP subtypes. Overall, 78.3% subjects were always classified between the same three groups, and 98.6% between five- and four-cluster solutions. However, the NTD subjects in four-cluster analysis were dispersed into the three groups when the three-cluster analysis was applied, with low concordance between the four- and three-cluster solutions. These results suggest that the subtypes generated in the four-cluster solution exhibit ideal internal cohesion and external isolation.

Considering that the results obtained with cluster analysis are strongly dependent on the selection of variables and the number of clusters sought (Foltynie *et al*., 2002), it might be expected that our results would show some differences from those of previous studies (Graham and Sagar, 1999; Lewis *et al*., 2005; Reijnders *et al*., 2009). Kappa statistical analysis indicated poor consistency between our cluster analysis and the subtype system based on motor phenotype. This suggests that the motor phenotype, non-motor symptoms, age at disease onset, as well as disease progression rate variables may all play significant roles in the clinical classification of PD, and it is inappropriate to classify PD patients solely on the basis of their motor phenotypes.

When different types of cluster-analysis were explored, subtypes showed good constancy, particularly between the five- and four-cluster solutions. The

subjects belonging to the RDP, TD, and YO subtypes in the five-cluster analysis were always clustered into the same groups in the four- and three-cluster analyses. In Lewis *et al.* (2005)'s study, 72.5% were always classified between the same three groups (YO, TD, and NTD). A total of 88% of cases remained in the same groups between the four- and five-cluster solutions and 76% between the three- and five-cluster solutions. However, the 20 RDP cases generated in the five-cluster analysis were separated into diverse subgroups in the four-cluster analysis (2 in YO, 1 in TD, 2 in NTD, and 15 in RDP), and the three-cluster analysis (4 in YO, 14 in TD, and 2 in NTD). Only 12 subjects classified in the NTD with severe cognitive impairment subgroup in a five-cluster analysis were always classified together in four- and three-cluster analyses. Moreover, when four-cluster analysis was performed, each cluster contained at least two kinds of subtypes from five-cluster analysis. This may indicate that the choice and number of variables selected for inclusion in the present study, especially the NMS variables and ADL progression rate, maybe more efficacious and favorable than those used by Lewis *et al.* (2005).

NMS may predate the diagnosis of PD which is typically based on motor signs (Chaudhuri and Naidu, 2008). Olfactory deficits, sleep problems such as rapid-eye movement sleep behavior disorder, constipation, and depression have been strongly suggested as preclinical (motor) characteristics in PD, while restless legs syndrome, apathy, fatigue, and anxiety have also been suggested to have links with early-stage PD (Chaudhuri *et al*., 2006). Importantly, we noted that the clinical domains included in the cluster analysis varied between previous studies. To avoid missing essential domains in discriminating subtypes, we included sleep disorders, constipation, fatigue, and depression in the cluster analysis. We found that there was no clinically significant difference between subgroup classifications in the three-, four-, and five-cluster solutions. This may suggest that these NMS were common features of early-stage PD. However, the potential usefulness of these symptoms in PD classification should not be overlooked, since the more comprehensive NMS variables may partially explain the good consistency among the different cluster analysis solutions in our study.

Lewis *et al*. (2005) used a variable calculated by dividing total UPDRS score for sections I–III by the disease duration as the disease progression parameter, whereas the progression of the patients' activities of daily living was not analyzed separately. The recent systematic review (van Rooden *et al*., 2010) of researches on identification of PD subtypes using cluster analysis showed that the variable of the patients' ADL was used in Reijnders (2009)' study, but not the progression of it. In the present study, the UPDRS total score part II/disease duration was applied as a variable for PD disease progression, and revealed significant differences among those subgroups. This result was supported by Harrison *et al*. (2009), which suggested that the UPDRS total score part II showed a stronger correlation with disease duration than other sections of the UPDRS. The UPDRS part II score/disease duration may be used as a valid marker of PD progression. Axial symptoms have been also considered as an important marker of PD progression. In the studies of PD motor patterns by van Rooden *et al*. (2009a; 2009b), the axial symptoms characterized by PIGD clearly reflected disease severity, which potentially provided a new basis for monitoring disease progression in PD. The NTD subtype showed the highest UPDRS PIGD score, followed by the RDP subtype. On the other hand, the RDP subtype exhibited the fastest disease progression, followed by NTD. When pair-wise cluster comparisons were conducted, no significant difference was found in the domains of the UPDRS PIGD score or disease progression between these two subtypes, suggesting that PIGD was closely related to disease progression.

There was no significant difference in UPDRS III tremor score between subtypes, but a clear difference was found in the ratio of tremor to non-tremor score. This may indicate that tremor is common for the majority of PD subjects; however, tremor-dominance could be applied as a classification variable.

Our four-subtype classification and definition of subtypes (YO, TD, NTD, and RDP) were in consistency with the conclusions of Lewis *et al*. (2005) and Reijnders *et al*. (2009). Our study identified a subtype of PD subjects with young onset of disease, which was also in agreement with other previous studies (Giovannini *et al*., 1991; Hughes *et al*., 1993). The YO subtype exhibited the youngest age at disease onset, with a disease progression rate similar to that of

the TD subtype. The ratio of tremor to non-tremor score of the TD subtype was significantly higher than those of the other subtypes, with a relatively low disease progression rate, in accordance with previous studies (Jankovic *et al*., 1990). The mean UPDRS III rigidity, hypokinesia, and PIGD scores of the NTD subtype were all higher than those of other subtypes. The RDP subtype exhibited the fastest rate of disease progression, showing not only a rapid rate of motor disease progression, but also a rapid ADL progression rate. The previous two studies (Lewis *et al*., 2005; Reijnders *et al*., 2009) included largely similar variables in the cluster analysis, and concluded four more or less similar PD subtypes (van Rooden *et al*., 2010). The present study replicated most of their results but using more variables in cluster analysis. Although these three studies differ in sample characteristics and assessment instruments, the consistency of the results suggests reliability of the four-subtype classification method.

In the latest study, Post *et al.* (2008) described three subgroups (a younger onset group, an intermediate older onset group with more anxiety and depressive symptoms, and an oldest onset group with more motor impairment and higher rate of progression) in a group of newly diagnosed PD (H-Y: 1–3) subjects. The first and third subtypes were in line with our results. The discrepancies of psychological assessment instruments and demographic characters may account for the difference in anxiety and depression statement between studies. Neither Post *et al*. (2008) nor Graham and Sagar (1999) could confirm the TD and NTD. The possible explanation for these discrepancies could be that they did not use the motor phenotype scoring system (tremor score versus non-tremor score) as we did.

Several limitations of the current study should be considered. First, the data-driven subtype classification requires validation with detailed clinicopathological data, since previous study (Jellinger, 2002) has suggested different neuropathological manifestations for different motor symptoms. Second, time variables of onset of the clinical features, which may play important roles in PD classification (Selikhova *et al.*, 2009), were not used in our study. In addition, the MMSE scale used in our study may not have been sensitive enough to identify mild cognitive impairment of PD subjects in the early stages. Nazem *et al.* (2009) used the Montreal cognitive assessment (MoCA) scale, revealing that cognitive dysfunction was common in patients with early-stage PD.

The present study identified the existence of clinical heterogeneity within the early clinical stages of PD using a data-driven approach. It suggested that Chinese PD patients in the early stages could be classified into four different subtypes: NTD, RDP, TD, and YO. Our results indicated that subtypes generated with a four-cluster solution may have ideal internal cohesion and external isolation. A longitudinal assessment of these PD patients, along with pathological validation through post mortem analysis, would be useful for confirming the present findings. If the defined subtypes in this cluster analysis can be confirmed by post-mortem examination, the existence of clinical subtypes is likely to be important in predicting prognosis and optimal therapy.

References

Chaudhuri, K.R., Naidu, Y., 2008. Early Parkinson's disease and non-motor issues. *J. Neurol.*, **255**(s5):33-38. [doi:10.1007/s00415-008-5006-1]

Chaudhuri, K.R., Healy, D.G., Schapira, A.H., 2006. Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol.*, **5**(3):235-245. [doi:10.1016/S1474-4422(06)70373-8]

Everitt, B.S., Landau, S., Leese, M., 2001. Cluster Analysis, 4th Ed. Hodder Headline Group, London.

Fahn, S., Elton, R.L., Members of the UPDRS Development Committee, 1987. Unified Parkinson's Disease Rating Scale. *In*: Fahn, S., Marsden, C.D., Calne, D.B., Goldstein, M., (Eds.), Recent Developments in Parkinson's Disease. Vol. 2, McMillan Health Care Information, Florham Park, New Jersey, p.153-163.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.*, **12**(3):189-198. [doi:10.1016/0022-3956(75)90026-6]

Foltynie, T., Brayne, C., Barker, R.A., 2002. The heterogeneity of idiopathic Parkinson's disease. *J. Neurol.*, **249**(2):138-145. [doi:10.1007/PL00007856]

Gibb, W.R., Lees, A.J., 1988. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry*, **51**(6):745-752. [doi:10.1136/jnnp.51.6.745]

Giovannini, P., Piccolo, I., Genitrini, S., Soliveri, P., Girotti, F., Geminiani, G., Scigliano, G., Caraceni, T., 1991. Early-onset Parkinson's disease. *Mov. Disord.*, **6**(1):36-42. [doi:10.1002/mds.870060107]

Golbe, L.I., 1993. Risk factors in young-onset Parkinson's disease. *Neurology*, **43**(9):1641-1643.

Graham, J.M., Sagar, H.J., 1999. A data-driven approach to the study of heterogeneity in idiopathic Parkinson's disease: identification of three distinct subtypes. *Mov. Disord.*, **14**(1):10-20. [doi:10.1002/1531-8257(199901)14:1<10::AID-MDS1005>3.0.CO;2-4]

Hamilton, M., 1960. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry*, **23**(1):56-62. [doi:10.1136/jnnp.23.1.56]

Harrison, M.B., Wylie, S.A., Frysinger, R.C., Patrie, J.T., Huss, D.S., Currie, L.J., Wooten, G.F., 2009. UPDRS activity of daily living score as a marker of Parkinson's disease progression. *Mov. Disord.*, **24**(2):224-230. [doi:10.1002/mds.22335]

Hoehn, M.M., Yahr, M.D., 1967. Parkinsonism: onset, progression and mortality. *Neurology*, **17**(5):427-442.

Hughes, A.J., Daniel, S.E., Blankson, S., Lees, A.J., 1993. A clinicopathologic study of 100 cases of Parkinson's disease. *Adv. Neurol.*, **50**(2):140-148.

Jankovic, J., McDermott, M., Carter, J., Gauthier, S., Goetz, C., Golbe, L., Huber, S., Koller, W., Olanow, C., Shoulson, I., *et al*., 1990. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. *Neurology*, **40**(10):1529-1534.

Jellinger, K.A., 2002. Recent developments in the pathology of Parkinson's disease. *J. Neural Transm. Suppl.*, (62):347-376.

Krupp, L.B., LaRocca, N.G., Muir-Nash, J., Steinberg, A.D., 1989. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch. Neurol.*, **46**(10):1121-1123.

Lewis, S.J., Dove, A., Robbins, T.W., Barker, R.A., Owen, A.M., 2003. Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. *J. Neurosci.*, **23**(15):6351-6356.

Lewis, S.J., Foltynie, T., Blackwell, A.D., Robbins, T.W., Owen, A.M., Barker, R.A., 2005. Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach. *J. Neurol. Neurosurg. Psychiatry*, **76**(3):343-348. [doi:10.1136/jnnp.2003.033530]

Li, G., Shen, Y.C., Chen, C.H., Li, S.R., Zhao, Y.W., Liu, M., Xu, L., Wang, L.X., Wang, Q., 1988. Preliminary application of MMSE in the aged of urban population in Beijing. *Chin. Mental Health J.*, **2**(1):13-18 (in Chinese).

Nazem, S., Siderowf, A.D., Duda, J.E., Have, T.T., Colcher, A., Horn, S.S., Moberg, P.J., Wilkinson, J.R., Hurtig, H.I., Stern, M.B., *et al*., 2009. Montreal cognitive assessment performance in patients with Parkinson's disease with "normal" global cognition according to mini-mental state examination score. *J. Am. Geriatr. Soc.*, **57**(2):304-308. [doi:10.1111/j.1532-5415.2008.02096.x]

Post, B., Speelman, J.D., de Haan, R.J., 2008. Clinical heterogeneity in newly diagnosed Parkinson's disease, *J. Neurol.*, **255**(5):716-722. [doi:10.1007/s00415-008-0782-1]

Reijnders, J.S., Ehrt, U., Lousberg, R., Aarsland, D., Leentjens, A.F., 2009. The association between motor subtypes and psychopathology in Parkinson's disease. *Parkinsonism Relat. Disord.*, **15**(5):379-382. [doi:10.1016/j.parkreldis.2008.09.003]

Selikhova, M., Williams, D.R., Kempster, P.A., Holton, J.L., Revesz, T., Lees, A.J., 2009. A clinico-pathological study of subtypes in Parkinson's disease. *Brain*, **132**(Pt 11):2947-2957. [doi:10.1093/brain/awp234]

Smyth, C., 2003. The pittsburgh sleep quality index. *Dermatol. Nurs.*, **15**(2):195-196.

Thompson, W.G., Longstreth, G.F., Drossman, D.A., Heaton, K.W., Irvine, E.J., Muller-Lissner, S.A., 1999. Functional bowel disorders and functional abdominal pain. *Gut*, **45**(Suppl. 2):II43-II47. [doi:10.1136/gut.45.2008.ii43]

van Rooden, S.M., Visser, M., Verbaan, D., Marinus, J., van Hilten, J.J., 2009a. Motor patterns in Parkinson's disease: a data-driven approach. *Mov. Disord.*, **24**(7):1042-1047. [doi:10.1002/mds.22512]

van Rooden, S.M., Visser, M., Verbaan, D., Marinus, J., van Hilten, J.J., 2009b. Patterns of motor and non-motor features in Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry*, **80**(8):846-850. [doi:10.1136/jnnp.2008.166629]

van Rooden, S.M., Heiser, W.J., Kok, J.N., Verbaan, D., van Hilten, J.J., Marinus, J., 2010. The identification of Parkinson's disease subtypes using cluster analysis: a systematic review. *Mov. Disord.*, **25**(8):969-978. [doi:10.1002/mds.23116]

Williams, L.N., Seignourel, P., Crucian, G.P., Okun, M.S., Rodriguez, R.L., Skidmore, F.M., Foster, P.S., Jacobson, C.E.4th, Romrell, J., Bowers, D., *et al*., 2007. Laterality, region, and type of motor dysfunction correlate with cognitive impairment in Parkinson's disease. *Mov. Disord.*, **22**(1):141-145. [doi:10.1002/mds.21220]

Zetusky, W.J., Jankovic, J., Pirozzolo, F.J., 1985. The heterogeneity of Parkinson's disease: clinical and prognostic implications. *Neurology*, **35**(4):522-526.