Heterogeneity in progression of prodromal features in Parkinson's disease

Schrag A FRCP, PhD[1*], Zhelev S S, MSc[1], Hotham S PhD[2], Merritt R D.Phil[2], Khan K MSc[1], Graham L. Ms[3]

[1]UCL Institute of Neurology, Royal Free Campus, University College London, London NW3 2PF; [2]Centre for Health Services Studies, University of Kent, [3]European Parkinson's Disease Association

*Corresponding author

Word count: abstract: 249, manuscript 1,831, 4 tables, 1 figure
Running title: Symptom patterns in prediagnostic PD
Keywords: Parkinson's disease; Prediagnostic phase; Subtypes; symptom complex; progression

Address for correspondence: Prof. Anette Schrag, Department of Clinical Neurosciences, UCL Institute of Neurology, Royal Free Campus, University College London, London NW3 2PF; tel: (+44) 20 7794 0500, a.schrag@ucl.ac.uk

Relevant conflicts of interest/financial disclosures: None
Funding sources for study: The My PD Journey was supported by AbbVie Inc.. AS was supported by the National Institute for Health Research UCL/H Biomedical Research Centre and the EU Joint Neurodegenerative Diseases Research Programme

Abstract

Background In the pre-diagnostic phase of Parkinson's disease (PD), a range of motor and non-motor symptoms can occur. However, there is considerable variability in their onset and currently little information exists on the pattern of progression of clinical features before diagnosis.

Methods We analysed data from a survey amongst patients with PD from 11 European countries by the European Parkinson's Disease Association. They completed questions on first occurrence of 21 pre-diagnostic features. A principal component analysis (PCA) with varimax rotation was performed to determine the co-occurrence of these features.

Findings 1,467 patients were included. Changes in movement were the most commonly reported features up to 4 years before diagnosis. However, at five or more years before diagnosis loss of sense of smell, sleep problems, fatigue and other non-motor features had been experienced most frequently. PCA of pre-diagnostic features' duration revealed three factors with eigenvalues over Kaiser's criterion of 1: a) a neuropsychiatric factor comprised of anxiety, depression, apathy, stress, and sleep problems; b) an axial factor defined by difficulty eating and/or swallowing problems, freezing, and falls/balance problems; and c) a motor factor with additional non-motor features. Bladder/bowel problems and tremor had low factor loadings on all components. However, in those with disease duration less than 5 years the autonomic features were associated with the axial factor and tremor loaded on both the motor and psychiatric symptom factors.

Interpretation The identified symptom complexes in the pre-diagnostic stage of PD may be reflective of a shared pattern of pathological disease progression.

Introduction

Non-motor and subtle motor features of Parkinson's disease (PD) can begin several years before a diagnosis of PD is made (1). However, there is considerable inter-individual variability and whilst some patients experience predominantly tremor or motor problems before diagnosis, others have olfactory loss, autonomic, cognitive, sleep-related, or psychiatric features, and these initial symptoms may reflect early involvement of different pathological areas (2) (3) (4). In established PD, subgroups with different clinical phenotypes, reflecting underlying sequential biological pathways and clinical progression rates, have been proposed (3). However, there is little information on the pattern and simultaneous occurrence of different symptoms in the pre-diagnostic phase. In an attempt to address this gap in knowledge we analysed data from a large number of patients with PD reporting the duration of their first symptoms before diagnosis to identify patterns of symptom progression in the prediagnostic phase.

Methods

Data were extracted from a survey conducted by the European Parkinson's Disease Association (EPDA) in 11 European countries (5). This included questions on first symptoms and their duration before diagnosis. Participants were recruited through PD associations in Germany, France, Netherlands, Sweden, UK, Slovenia, Spain, Italy, Hungary, Ireland, and Denmark. The survey was completed online in all countries apart from patients in Slovenia, where hard copies were distributed because of restricted access to the internet. Data were collected from 1st November 2014 to 12th January 2015.

Assessments

The self-administered survey included questions on demographics, country, disease duration and questions about the presence of symptoms and their duration before diagnosis. These included loss of smell or taste, sleep problems, low blood pressure or dizziness, bladder and bowel problems, skin and/or sweating problems, pain, thinking or memory problems, anxiety, apathy, depression, feeling of stress, slowness of movement, changes in movements (including arm swing), falls (balance problems), freezing, communication problems (including speech and handwriting), difficulty eating and/or swallowing, muscle cramps, rigidity (stiffness), fatigue and tremor. For each symptom, duration of symptoms before diagnosis was reported as: less than one year, 1 to 2 years, 3 to 4 years, or 5 years or more before diagnosis, or symptom not preceding diagnosis.

Statistical analysis

Descriptive data are presented as percentages and medians for each symptom. A factor analysis of the 21 pre-diagnostic symptoms using the principal component method with varimax rotation was performed to establish the underlying dimensions of co- occurrence, which might reflect underlying pathological substrates. Factor loadings were determined using a cut-off for at least fair loading (<0.45) (6, 7). Factors with eigenvalues over Kaiser's criterion of 1 were retained and the percentage of variance of the data explained calculated (Figure 1 supplementary material). As recall bias may affect the results particularly in those with disease onset more than 5 years ago, we also undertook at sensitivity analysis excluding those with a disease duration of 5 years or more.

Ethics approval for the analysis was given by the UCL Research Ethics Committee (14295/001).

Results

1775 participants completed the survey. Data for the analysis were available for 1467 patients excluding those that did not fully complete the scale of 21 symptoms (n=130) or gave impossible or contradictory information on age and disease duration (n=178). Table 1 below shows the demographic profile of participants and table 1 supplementary material that of participants with <5 years duration only.

Symptoms experienced before diagnosis

The number of patients that had experienced each symptom before diagnosis is presented in figure 1, and their occurrence by time before diagnosis in table 2. The most commonly reported symptoms before diagnosis overall were changes in gait (80.2 %), slowness of movement (60.5 %), tremor (57.3 %), stiffness/rigidity (54.7 %), fatigue (53.9 %) and communication problems (including speech/handwriting), (53.5 %). At more than 5 years before diagnosis, on the other hand, the most frequently experienced symptom was loss of smell (15.1%), followed by sleep problems (11.5%), fatigue (11.3%), stress (11%) and bladder/bowel problems (10.4%). Tremor and slowness of movement most commonly occurred in the 2 years before diagnosis. In the subgroup of those with <5 years duration results were similar (suppl table 2).

Factor Analysis of pre-diagnostic symptoms

Exploratory factor analysis revealed three factors with eigenvalues over Kaiser's criterion of 1 indicating co-occurrence of symptoms: *A neuropsychiatric symptom*

complex of anxiety, depression, apathy, stress, and sleep problems; an *axial motor symptom complex* including freezing, falls/balance problems, difficulty eating and/or swallowing, slowness of movement and communication (speech/handwriting) problems; and a *motor factor that also included sensory, cognitive and autonomic nonmotor features,* encompassing slowness of movement, fatigue, rigidity/stiffness, muscle cramps, pain, changes in movement (including arm swing), speech/handwriting problems, loss of smell or taste, thinking or memory problems, stress, sleep disturbances, skin and/or sweating problems, and low blood pressure or dizziness. *Tremor* and *bladder/bowel problems* had low factor loading on all components. However, in the sensitivity analysis restricted to those with a diagnosis within 5 years, bladder and bowel problems and low blood pressure./dizziness also loaded on the axial factor, and tremor loaded on both motor and psychiatric symptom factors. The motor factor split into two factors characterised by slowness of movement and fatigue: one including rigidity, muscle cramps, pain, sleeping problems and stress, and another including changes in movement (including arm swing), speech/handwriting problems, tremor, thinking or memory problems and loss of sense of smell or taste. Factor loadings are shown in table 3 (whole cohort) and 4 (participants within 5 years of diagnosis).

Discussion

The symptoms most frequently noted by patients in the pre-diagnostic phase of PD, when reported retrospectively in this large cohort of patients with PD, were related to disturbances of motor function, reflecting the classical features leading to a diagnosis of PD. Tremor and slowness most commonly occurred relatively shortly before diagnosis. However, the feature most frequently reported more than 5 years before

diagnosis was loss of smell followed by other pre-diagnostic features, including sleep disturbances, fatigue, stress, and bladder and bowel problems, before slowness and changes in movement were noted. Many of these, such as fatigue, bladder and bowel problems, and sleep disturbances, are frequently reported in non-PD patients, but are also clinical features that can predate motor features in the general population (1). Whilst our study design does not allow definite attribution of these complaints to PD, their occurrence in the five years before PD diagnosis is consistent with previous reports (1). Loss of sense of smell in the absence of causative local pathology or medication is relatively specific as a preclinical feature of neurodegenerative disease, but other neurodegenerative diseases can also be associated with this feature (8).

There were at least three distinct initial symptom complexes in this population: Neuropsychiatric features (anxiety, depression, apathy, sleep disturbances and stress) were experienced together, consistent with their known overlapping clinical phenomenology and pathophysiology. Similarly, axial features (falls/balance problems, difficulty eating and/or swallowing, communication (speech/handwriting) problems, and slowness of movement) which may be seen together in more aggressive subtypes of parkinsonism occurred together, suggesting a shared underlying pathology, possibly within midbrain neurodegeneration (9). This explanation is also suggested by the finding that in the analysis restricted to those with a shorter time since diagnosis the autonomic features of low blood pressure or dizziness and bladder and bowel problems loaded onto the same factor as axial features. The largest factor included all other features related to motor impairment as well as cognitive, sensory and autonomic features. However, the sensitivity analysis suggested that motor features related to rigidity and pain, as well as sleep

disturbances occur in a different pattern than those related to other motor features including handwriting, reduced arm swing and tremor as well as loss of smell or taste. There was some overlap between the factors. Experiences of sleep disturbances and of stress occurred together with both the neuropsychiatric features and with the features related to motor impairment. This is likely to reflect the multifactorial nature of these features. Similarly, reports of slowness and of the combined question on communication difficulties due to speech and handwriting problems loaded on several factors, reflecting the broadness of the questions. Thinking and memory problems loaded comparably on all motor factors indicating indicating the lack of specificity of this question. Report of tremor did not load highly on any of the factors in the overall cohort, suggesting that it appears to develop at a different time than other pre-diagnostic features of PD. However, in the analysis restricted to those with a shorter disease duration, who are less likely to be affected by recall bias, tremor occurrence was associated with both apendicular motor features and psychiatric features, including anxiety, which may enhance an existing subtle tremor.

Whilst we are not aware of other studies exploring the temporal relationship between occurrence of prediagnostic features of PD, our results of retrospective reports of these features in patients with PD are comparable to others, with a range of pre-diagnostic features reportedly having occurred several years before diagnosis, without differences between different motor subtypes (Pont-Sunyer, Hotter et al. 2015). In addition to our own data based on primary care presentations before diagnosis of PD (1), others reported that pre-diagnostic features were experienced by patients with PD 10-15 years before diagnosis (10), and reported retrospectively that hyposmia, constipation, sleep disturbances, depression and anxiety had been

present many years before motor features (11-15). These features have been used successfully to help predict occurrence of PD as components of the MDS research criteria for prodromal PD (Mahlknecht, Gasperi et al. 2018; Fereshtehnejad, Montplaisir et al. 2017, Pilotto, Heinzel et al. 2017, Mahlknecht, Gasperi et al. 2018)

Limitations

The main limitation of this study is that it is a study of retrospectively reported initial symptoms in patients with a range of different disease duration, which may be subject to recall bias and individual experiences. In addition, there was no control group and it is likely that not all of the symptoms were due to PD. However, all features surveyed have been previously reported to be increased in patients with PD in the prediagnostic phase(1) and were attributed to PD by patients who were later diagnosed with PD. To our knowledge this is the first analysis of the temporal co-occurrence of prediagnostic motor and non-motor features of PD. The large sample size enabled robust conclusions on when prediagnostic features of PD are first experienced by patients with a later diagnosis of PD.

The results of this study also suggest that there are distinct combinations of clinical features in the prediagnostic phase of PD, which occur in a similar timeframe before diagnosis. These may reflect initial involvement of different underlying pathological areas and pathophysiological progression patterns. Assessing occurrence of these subgroups of prediagnostic features of PD may be helpful to differentially assess disease progression in this phase.

Table 1.
Participant characteristics

Demographic Profile				Disease Duration		
	M (SD)		*Mdn (IQR)*		*M (SD)*	*Mdn (IQR)*
Age	65.43 (9.69)		67 (12)	Age when diagnosed	58.65 (9.92)	60 (14)
				Disease duration	7.79 (5.67)	6 (7)
Gender	*n*	(%)				
Males	791	53.9 %				
Females	676	46.1 %				
				Length of diagnosis	*n*	(%)
Area	*n*	(%)				
Rural	278	19 %		Less than 1 year	143	9.7 %
Town	530	36.2 %		At least 1 year but less than 2 years	134	9.1 %
City	658	44.9 %		At least 2 years but less than 3 years	172	11.7 %
				At least 3 years but less than 5 years	252	17.2 %
Employment	*n*	(%)		At least 5 years but less than 10 years	436	29.7 %
Employed	292	19.9 %		More than 10 years	329	22.4 %
Unemployed	1175	80.1 %				

Note. *M* = Mean; *SD* = Standard deviation; *Mdn* = Median; *IQR* = Interquartile range; *n* = Sample size.

Table 2. Number (%) of patients that experienced each symptom before diagnosis by time before onset.

Symptom	5 years or more (%)	3-4 years (%)	1 to 2 years (%)	Less than 1 year (%)	Total n without symptom (%)
Loss of smell or taste	222 (15.1)	134 (9.1)	134 (9.1)	161 (11)	815 (55.6)
Sleep problems	168 (11.5)	122 (8.3)	182 (12.4)	156 (10.6)	838 (57.1)
Fatigue	166 (11.3)	157 (10.7)	250 (17)	218 (14.9)	676 (46.1)
Stress	162 (11)	137 (9.3)	188 (12.8)	144 (9.8)	834 (56.9)
Bladder and bowel problems	153 (10.4)	103 (7)	128 (8.7)	85 (5.8)	997 (68)
Changes in movement	138 (9.4)	211 (14.4)	492 (33.5)	336 (22.9)	290 (19.8)
Pain	135 (9.2)	115 (7.8)	182 (12.4)	160 (10.9)	874 (59.6)
Rigidity/stiffness	128 (8.7)	144 (9.8)	267 (18.2)	264 (18)	662 (45.1)
Low blood pressure or dizziness	115 (7.8)	84 (5.7)	120 (8.2)	121 (8.2)	1026 (69.9)
Depression	108 (7.4)	83 (5.7)	119 (8.1)	98 (6.7)	1059 (72.2)
Muscle cramps	105 (7.2)	118 (8)	201 (13.7)	200 (13.6)	841 (57.3)
Skin and/or sweating problems	105 (7.2)	81 (5.5)	113 (7.7)	97 (6.6)	1069 (72.9)
Tremor	105 (7.2)	107 (7.3)	262 (17.9)	365 (24.9)	626 (42.7)
Slowness of movement	101 (6.9)	146 (10)	334 (22.8)	305 (20.8)	580 (39.5)
Anxiety	90 (6.1)	65 (4.4)	83 (5.7)	121 (8.2)	1096 (74.7)
Communication (incl. speech or handwriting)	89 (6.1)	133 (9.1)	270 (18.4)	292 (19.9)	682 (46.5)
Thinking or memory problems	73 (5)	96 (6.5)	169 (11.5)	193 (13.2)	935 (63.7)
Falls/balance problems	64 (4.4)	81 (5.5)	142 (9.7)	170 (11.6)	1009 (68.8)
Apathy	46 (3.1)	44 (3)	98 (6.7)	84 (5.7)	1195 (81.5)
Difficulty eating and/or swallowing	39 (2.7)	19 (1.3)	94 (6.4)	117 (8)	1196 (81.5)
Freezing	33 (2.2)	60 (4.1)	97 (6.6)	135 (9.2)	1140 (77.7)

Table 3. Factor loadings for each clinical feature

	Component		
Symptom	1	2	3
Rigidity/stiffness	**.686**	.106	.321
Slowness of movement	**.634**	.096	**.466**
Muscle cramps	**.626**	.273	.123
Fatigue	**.617**	.368	.229
Changes in movements, incl. arm swing	**.590**	.046	.326
Stress	**.583**	**.539**	.010
Pain	**.578**	.308	.157
Loss of smell or taste	**.546**	.031	.111
Thinking or memory problems	**.535**	.232	.372
Communication (incl. speech or handwriting)	**.507**	.095	**.490**
Sleep problems	**.499**	**.475**	.211
Skin and/or sweating problems	**.473**	.410	.203
Low blood pressure or dizziness	**.462**	.244	.284
Tremor/shaking	.313	.305	.052
Anxiety	.141	**.804**	.170
Depression	.214	**.775**	.173
Apathy	.004	**.692**	.370
Bladder and bowel problems	.308	.365	.339
Difficulty eating and/or swallowing	.132	.278	**.707**
Freezing	.248	.195	**.700**
Falls (balance problems)	.330	.191	**.657**

Table 4. Factor loadings for each clinical feature in those within 5 years of diagnosis

	Component			
Symptom	1	2	3	4
Rigidity/stiffness	**.612**	.027	.244	.441
Slowness of movement	**.459**	.025	.351	**.553**
Muscle cramps	**.712**	.143	.160	.152
Fatigue	**.491**	.312	.219	**.467**
Changes in movements, incl. arm swing	.328	.106	.228	**.558**
Stress	**.490**	**.521**	.082	.328
Pain	**.708**	.181	.219	.066
Loss of smell or taste	-.028	.117	.188	**.653**
Thinking or memory problems	.305	.229	.352	**.463**
Communication (incl. speech or handwriting)	.280	.135	.294	**.553**
Sleep Problems	**.548**	**.470**	.257	.092
Skin and/or sweating problems	**.513**	.343	.242	.127
Low blood pressure or dizziness	.314	.081	**.525**	.205
Tremor/shaking	.042	**.478**	-.174	**.496**
Anxiety	.211	**.792**	.181	.121
Depression	.244	**.752**	.191	.163
Apathy	.054	**.685**	.416	.084
Bladder and bowel problems	.234	.313	**.550**	.047
Difficulty eating and/or swallowing	.017	.252	**.616**	.248
Freezing	.230	.103	**.631**	.192
Falls (balance problems)	.321	.092	**.576**	.224

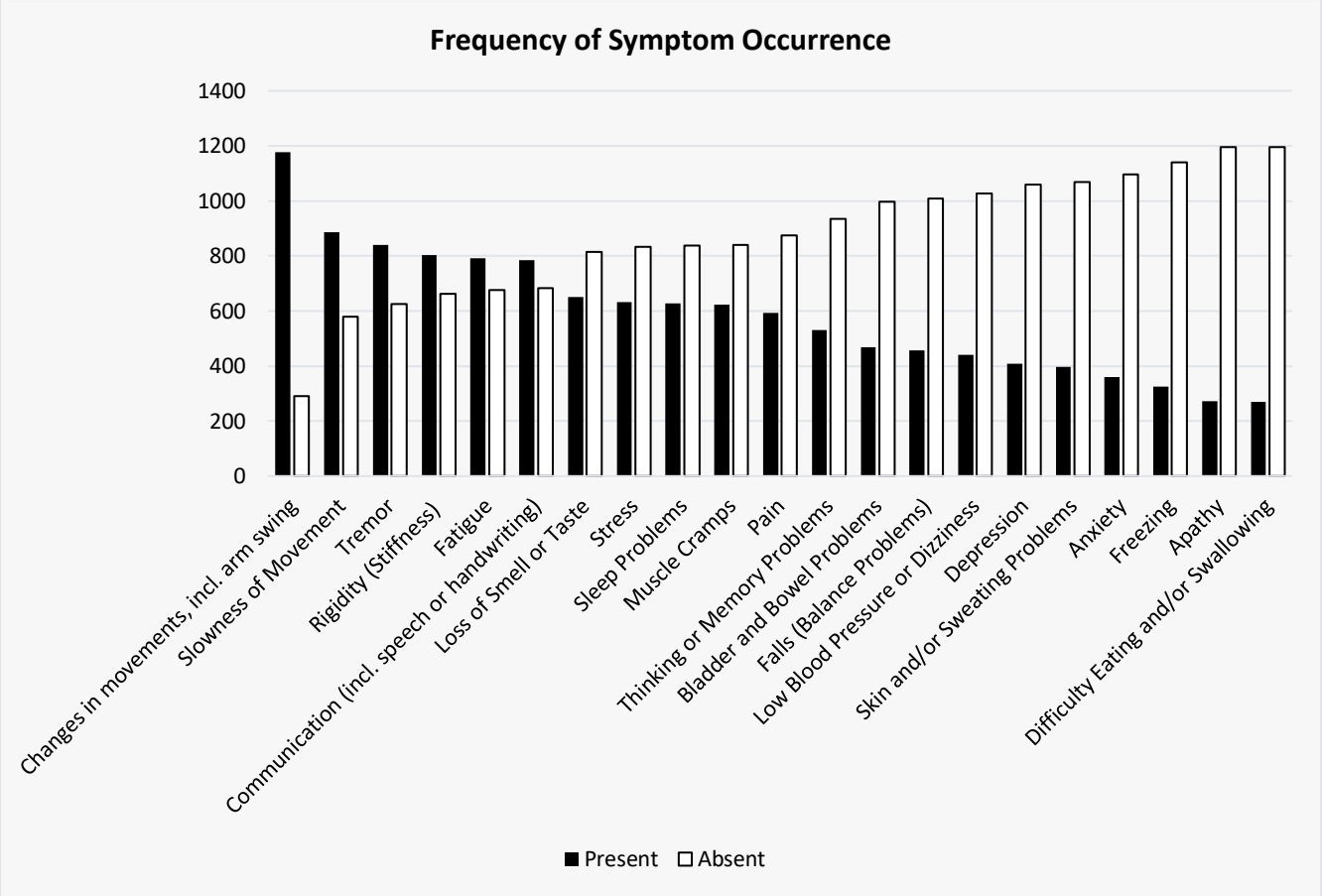

Figure 1. Number of patients who had (black) and had not experienced (white) each of the symptoms.

References

1. Schrag A, Horsfall L, Walters K, Noyce A, Petersen I. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. Lancet Neurol. 2015;14(1):57-64.
2. Fereshtehnejad SM, Romenets SR, Anang JB, Latreille V, Gagnon JF, Postuma RB. New Clinical Subtypes of Parkinson Disease and Their Longitudinal Progression: A Prospective Cohort Comparison With Other Phenotypes. JAMA neurology. 2015;72(8):863-73.
3. Mu J, Chaudhuri KR, Bielza C, de Pedro-Cuesta J, Larranaga P, Martinez-Martin P. Parkinson's Disease Subtypes Identified from Cluster Analysis of Motor and Non-motor Symptoms. Frontiers in aging neuroscience. 2017;9:301.
4. Del Tredici K, Braak H. Review: Sporadic Parkinson's disease: development and distribution of alpha-synuclein pathology. Neuropathology and applied neurobiology. 2016;42(1):33-50.
5. Schrag A, Modi S, Hotham S, Merritt R, Khan K, Graham L, et al. Patient experiences of receiving a diagnosis of Parkinson's disease. J Neurol. 2018.
6. Comrey AL, Lee, H. B. . A first course in factor analysis. Psychology Press. 2013.
7. Tabachnick BG, Fidell, L. S. . Using multivariate statistics. Allyn & Bacon/Pearson Education. 2007.
8. Hawkes CH. The prodromal phase of sporadic Parkinson's disease: does it exist and if so how long is it? Mov Disord. 2008;23(13):1799-807.
9. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, et al. Parkinson disease. Nat Rev Dis Primers. 2017;3:17013.
10. Gaenslen A, Swid I, Liepelt-Scarfone I, Godau J, Berg D. The patients' perception of prodromal symptoms before the initial diagnosis of Parkinson's disease. Mov Disord. 2011;26(4):653-8.
11. Walter U, Kleinschmidt S, Rimmele F, Wunderlich C, Gemende I, Benecke R, et al. Potential impact of self-perceived prodromal symptoms on the early diagnosis of Parkinson's disease. J Neurol. 2013;260(12):3077-85.
12. Mahlknecht P, Gasperi A, Djamshidian A, Kiechl S, Stockner H, Willeit P, et al. Performance of the Movement Disorders Society criteria for prodromal Parkinson's disease: A population-based 10-year study. Mov Disord. 2018;33(3):405-13.
13. Pont-Sunyer C, Hotter A, Gaig C, Seppi K, Compta Y, Katzenschlager R, et al. The onset of nonmotor symptoms in Parkinson's disease (the ONSET PD study). Mov Disord. 2015;30(2):229-37.
14. Fereshtehnejad SM, Montplaisir JY, Pelletier A, Gagnon JF, Berg D, Postuma RB. Validation of the MDS research criteria for prodromal Parkinson's disease: Longitudinal assessment in a REM sleep behavior disorder (RBD) cohort. Mov Disord. 2017;32(6):865-73.
15. Pilotto A, Heinzel S, Suenkel U, Lerche S, Brockmann K, Roeben B, et al. Application of the movement disorder society prodromal Parkinson's disease research criteria in 2 independent prospective cohorts. Mov Disord. 2017;32(7):1025-34.