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The influence of age and gender on motor and non-motor features of early Parkinson's disease: Initial findings from the Oxford Parkinson Disease Center (OPDC) discovery cohort

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ABSTRACT

Background: Identifying factors influencing phenotypic heterogeneity in Parkinson's Disease is crucial for understanding variability in disease severity and progression. Age and gender are two most basic epidemiological characteristics, yet their effect on expression of PD symptoms is not fully defined. We aimed to delineate effects of age and gender on the phenotype in an incident cohort of PD patients and healthy controls from the Oxford Parkinson Disease Centre (OPDC).

Methods: Clinical features, including demographic and medical characteristics and non-motor and motor symptoms, were analyzed in a group of PD patients within 3 years of diagnosis and a group of healthy controls from the OPDC cohort. Disease features were stratified according to age and compared between genders, controlling for effects of common covariates.

Results: 490 PD patients and 176 healthy controls were analyzed. Stratification by age showed increased disease severity with age on motor scales. Some non-motor features showed similar trend, including cognition and autonomic features. Comparison across genders highlighted a pattern of increased severity and greater symptom symmetricality in the face, neck and arms in men with women having more postural problems. Amongst the non-motor symptoms, men had more cognitive impairment, greater rate of REM behavior disorder (RBD), more orthostatic hypotension and sexual dysfunction.

Conclusions: Age in PD is a strong factor contributing to disease severity even after controlling for the effect of disease duration. Gender-related motor phenotype can be defined by a vertical split into more symmetrical upper-body disease in men and disease dominated by postural symptoms in women.

1. Introduction

There is a growing recognition that Parkinson disease (PD) has phenotypic heterogeneity [1] in its motor and non-motor manifestations [2]. Age and gender are two basic characteristics that may influence disease phenotype, either through disease-independent factors or differences in underlying pathology. One therefore wants to examine age and gender related differences in a large incident cohort of patients with detailed phenotypic data.

Oxford Parkinson Disease Center (OPDC, http://opdc.medsci.ox.ac.uk) was established in 2009 with funding from the Parkinson UK Monument Discovery Award and brings together world-leaders in clinical neurology, neuroepidemiology, neuroimaging, proteomics, genomics, molecular genetics, transgenic PD models, neuropharmacology, neurophysiology and neuropathology. The OPDC cohort is a prospective, longitudinal study that has recruited patients with early idiopathic Parkinson Disease, healthy controls and participants at risk of PD. We present an analysis of age and gender effects on the PD phenotype with an overview of the study protocol in our cohort.

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2. Methods

2.1. Participants

Study participants are recruited from neurology clinics across the Thames Valley area covering a population of 2.4 million. Participating centers include: Oxford, Reading, Newbury, Wexham Park, High Wycombe, Aylesbury, Milton Keynes, Kettering, Northampton, Banbury and Swindon. Neurologists, PD nurses, geriatricians and GP's from participating hospitals are asked to identify all idiopathic PD cases who were diagnosed within the last three years according to the UK PD Brain Bank criteria (UKPD-BB) by a neurologist or geriatrician with a specialist interest in PD. All participating clinicians are regularly contacted to ensure screening of incident cases diagnosed since study onset. Eligible cases are approached by post and asked to contact the OPDC if they are willing to take part in the study. Exclusion criteria for participation are: non-idiopathic parkinsonism, dementia preceding PD by one year suggestive of Dementia with Lewy Bodies, cognitive impairment precluding informed consent. Atypical parkinsonian features are additionally screened for by the study neurologist using the NINDS Parkinson's tool (see Supplementary Table 1).

Healthy controls are recruited from spouses and friends of PD participants and approached by the patients themselves. The PD at-risk group comprises first-degree relatives of PD patients and a smaller group of patients with REM behavior sleep disorder (RBD) diagnosed on polysomnography.

The study was undertaken with the understanding and written consent of each subject, with the approval from the Berkshire Research Ethics Committee and in compliance with national legislation and the Declaration of Helsinki. Subjects may choose to withdraw at any time and need to agree to all aspects of the study.

2.2. Clinical assessment protocol

Patients were assessed in research clinics, by a nurse and a doctor, using a variety of questionnaires covering demographic information and motor and non-motor features of PD (questionnaire list in Supplementary Table 1). Cognitive assessments were administered in a standardized way by Dendron research nurses who had been trained by a clinical psychologist. Patients were also examined neurologically while on their usual medication and gave blood for DNA and serum biomarkers. Visits are scheduled every 18 months for 5 years initially, but the cohort is envisaged to continue for 10–20 years, subject to funding.

2.3. Statistical analysis

We have presented data from an interim analysis of the PD and control groups, including participants recruited between study onset in September/2010 up to August/2012. In the PD group, we have only included patients who were thought by the clinician to have a ≥90% likelihood of PD. Details of recoding of the raw variables are shown in the Supplementary Table 1. Demographic characteristics were compared using χ^2-test and *t*-test. Clinical characteristics requiring covariate adjustment were analysed using multivariable linear or logistic regression. To examine age and gender effects we classified PD subjects into three age groups (≤65, 65–75, >75 years) and stratified analyses by age and gender. Most comparisons were adjusted for age and gender and for additional variables thought to be potential confounders. Where the test variables varied by age, we undertook a formal Cochrane–Armitage test for trend. A conventional threshold of 0.05 was set for statistical significance, though given the large number of comparisons, results between 0.01 and 0.05 should be interpreted with caution as they may reflect a type I error due to multiple testing.

3. Results

In the analyzed period, 624 PD patients agreed to take part in our study, making up 57% of all approached subjects. Non-participants were significantly older than participants (mean (SD), age 73.0 (10.6) years, $p < 0.001$), but with no gender differences. Additionally, 176 healthy controls (HC) were recruited into the study in the above period.

3.1. Demographics and general medical history

Table 1 shows the demographics and general medical history of the two groups. The PD cohort was older and had more males, but did not differ from controls in ethnicity, handedness or marital status. We found no differences in past medical history but smoking and alcohol consumption before PD onset were less common in PD than HC whilst there were no differences for caffeine consumption. There were no differences in the risk of cardiovascular disease, all cancers, melanoma or gout. We could not compare the family history of PD between the two groups as control participants with any relatives with PD were re-assigned to our 'at-risk' cohort.

PD patients had lower socioeconomic status than controls (Supplemental Table 2). For example, they were less educated and

Table 1
Basic demographics and Past Medical and Family History. Comparison between PD and HC groups.

Basic demographics	PD group $N = 490$	HC group $N = 176$	*P* value
Age, (mean ± SD)	67.9 ± 9.3	64.3 ± 9.1	<0.001
Gender, (females, %)	37.6	63.6	<0.001
Ethnicity, (white:non-white, %)	98.4:1.6	98.3:1.7	0.57
Marital status, (married, %)	96.9	98.8	0.08[a]
Handedness, (right:left:both, %)	87.7:9.0:3.3	86.6:9.3:4.7	0.74
Past medical history			
Vascular risk factors, (%)	45.7	43.2	0.40[a]
Cerebrovascular disease, (%)	4.3	1.7	0.18[c]
Cardiovascular disease, (%)	12.7	4.6	0.06[c]
Cancers, (%)	9.2	8.0	
Males, (%)	11.4	7.8	0.56[c]
Females, (%)	5.4	8.0	0.17[c]
Melanoma, (%)	2.1	2.8	0.11[a]
Respiratory disease, (%)	11.6	9.1	0.20[c]
Rheumatoid arthritis, (%)	1.22	0.57	0.41[a]
Gout, (%)	6.4	4.0	0.72[a]
Ovarian resection before PD, (%)	12.9	12.2	0.88[a]
Depression diagnosis before PD, (%)	18.0	22.2	0.74[b]
Anxiety diagnosis before PD, (%)	12.9	14.2	0.51[b]
Caffeine consumption before PD, cups/day, (mean ± SD)	5.3 ± 3.6	5.0 ± 2.3	0.51[c]
Smoking before PD, (%)	39.1	44.3	0.008[c]
Alcohol consumption before PD, (%)	73.7	81.1	0.03[b]
Family history			
Patients with at least one 1st degree relative with PD, (%)	16.7	N/A	N/A
Patients with at least one 2nd degree relative with PD, (%)	9.2	N/A	N/A
Patients with at least one 1st or 2nd degree relatives with PD	23.7	N/A	N/A
Subjects with at least one 1st or 2nd degree relative with any neurological disorder, (%)	45.7	54.6	0.26[a]

[a] Adjusted for age, gender.
[b] Adjusted for age, gender, anxiety.
[c] Adjusted for age, gender and caffeine consumption (for smoking) or smoking (for caffeine consumption, cerebrovascular and cardiovascular disease).

less likely to own their house or be employed. There was no significant difference in types of medications taken before diagnosis of PD by patients and controls (Supplemental Table 2).

3.2. Disease onset, motor features and PD medication

The average disease duration since diagnosis was 1.74 years (Table 2) while duration since symptom onset was 3.36 years. The commonest symptom at diagnosis was bradykinesia, followed by tremor and postural problems. In 51% of patients the symptoms started on the left-hand side, while only 7% had symmetrical onset. The average UPDRS-III was 27.0 with 80% of patients classified as H&Y I–II – a consequence of recruiting patients with early disease. Out of four cardinal motor features tested by UPDRS-III, bradykinesia and rigidity scores were highest with postural scores in the middle and tremor scores lowest. Greater severity of postural problems than tremor was also reflected in higher rates of PIGD-type than tremor-type. The most severely affected body region were the arms, followed by legs, face and neck. Motor complications (UPDRS-IV) were infrequent with only 5% and 4% of patients manifesting dyskinesia and motor fluctuations, respectively.

Stratification by age (Table 2) revealed that rigidity at onset was less common in older patients while rate of postural problems increased with age. The UPDRS-III score and subscores (except rigidity), annualized UPDRS-III, symmetricality of symptoms and objective measures of severity (Peg-board, Get-up-and-go, Flamingo) significantly increased with age while UPDRS-IV decreased.

Analysis of gender effects on motor features (Table 2) showed that postural problems at onset were more common in women which was confirmed by higher postural scores in UPDRS-III, longer time on Get-up-and-go and greater proportion of women with PIGD subtype and H&Y $\geq$ 3. Bradykinesia at onset was more common amongst women but reached the same level as in men on the first visit. Rigidity was significantly higher in men, while total UPDRS-III showed a tendency in that direction. Men showed significantly higher UPDRS-III in the face, neck and arms with no difference in leg scores. Greater severity in the arms in men was reflected in poorer performance on all peg-board tests. Men had more symmetrical disease both on UPDRS-III and peg-board asymmetry index. There was no evidence that age or gender in this cohort influenced time from symptom onset to disease diagnosis, as it has been speculated that older patients and women may be slower to present to health care professionals.

Overall, we found that the most common UPDRS-II symptom (Table 3) was tremor, followed by axial symptoms (getting out of bed; walking and balance). Stratification by age (Table 3) revealed strong effects for dressing problems, turning in bed and getting out of bed. There were also very marked differences in medication so that older patients were more likely to be on levodopa and a higher dosage and far less likely to be on an agonist, though clinical

Table 2
Disease onset and motor symptoms stratified by age group and gender.

Dependent variable	Total $N = 490$	Age stratification				Gender stratification		
		$\leq$65 $N = 178$	>65, $\leq$75 $N = 204$	>75 $N = 108$	*P* for trend	Males $N = 306$	Females $N = 184$	*P* value
Disease onset								
Age at diagnosis, (mean ± SD)	66.1 ± 9.5	56.4 ± 6.7	68.6 ± 3.3	77.7 ± 3.8	<0.001[b]	66.1 ± 9.2	65.7 ± 9.9	0.71[a]
Age at onset, (mean ± SD)	64.5 ± 9.5	54.9 ± 6.7	66.8 ± 3.7	76.1 ± 4.1	<0.001[b]	64.8 ± 9.2	64.1 ± 10	0.29[a]
Duration since diagnosis (y), (mean ± SD)	1.74 ± 1.8	1.81	1.68	1.74	0.70[b]	1.7 ± 1.6	1.8 ± 2.2	0.71[a]
Duration since symptom onset (y), (mean ± SD)	3.36 ± 2.42	3.3 ± 2.6	3.4 ± 2.3	3.4 ± 2.4	0.70[b]	3.3 ± 2.3	3.5 ± 2.7	0.29[a]
Time from symptom onset to diagnosis (y), (mean ± SD)	1.67 ± 1.7	1.4 ± 1.4	1.8 ± 1.8	1.7 ± 1.8	0.19[b]	1.6 ± 1.7	1.7 ± 1.7	0.36[a]
Tremor at diagnosis, (%)	86.9	84.2	88	88.9	0.22[c]	87.2	86.4	0.83[d]
Rigidity at diagnosis, (%)	78.2	81.9	76.4	71	0.05[c]	76.5	81	0.24[d]
Bradykinesia at diagnosis, (%)	92.0	90.2	93.5	93.3	0.34[c]	89.9	95.6	0.05[d]
Postural problems at diagnosis, (%)	29.8	26	27.1	41	0.04[c]	25.5	36.8	0.03[d]
Symmetrical onset, (%)	6.5	3.5	6.9	5.8	0.76[c]	7.8	4.4	0.17[d]
UPDRS III								
Total UPDRS III, (mean ± SD)	27.0 ± 11.1	24.4 ± 9.3	26.8 ± 11.2	31.9 ± 12.3	<0.001[e]	27.7 ± 11.2	25.9 ± 11	0.07[f]
H&Y $\geq$3, (%)	7.8	2.2	5.9	20.4	<0.001[e]	5.2	12	0.007[f]
Rigidity scores, (score/number of items, mean ± SD)	1.06 ± 0.51	1 ± 0.5	1 ± 0.5	1.1 ± 0.6	0.10[e]	1.1 ± 0.5	1 ± 0.5	0.002[f]
Bradykinesia scores, (score/number of items, mean ± SD)	1.18 ± 0.6	1.1 ± 0.5	1.1 ± 0.6	1.3 ± 0.7	0.02[e]	1.2 ± 0.6	1.2 ± 0.6	0.49[f]
Postural scores, (score/number of items, mean ± SD)	0.55 ± 0.48	0.4 ± 0.3	0.5 ± 0.5	0.8 ± 0.6	<0.001[e]	0.5 ± 0.4	0.6 ± 0.5	0.06[f]
Tremor scores, (score/number of items, mean ± SD)	0.38 ± 0.29	0.3 ± 0.3	0.4 ± 0.3	0.4 ± 0.3	0.008[e]	0.4 ± 0.3	0.4 ± 0.3	0.27[f]
Motor subtype, (PIGD, %)	52	48.9	47.5	67.6	0.006[e]	48.4	59.2	0.02[f]
Face and neck score, (score/number of items, mean ± SD)	0.58 ± 0.39	0.5 ± 0.33	0.58 ± 0.37	0.73 ± 0.45	<0.001[e]	0.66 ± 0.40	0.45 ± 0.32	<0.001[e]
Arms score, (score/number of items, mean ± SD)	0.97 ± 0.40	0.92 ± 0.37	0.95 ± 0.40	1.08 ± 0.46	0.005[e]	1.00 ± 0.42	0.92 ± 0.37	0.025[e]
Legs score, (score/number of items, mean ± SD)	0.75 ± 0.45	0.71 ± 0.39	0.74 ± 0.48	0.84 ± 0.45	0.29[e]	0.75 ± 0.43	0.75 ± 0.47	0.922[e]
Symmetrical disease, (%)	25	16.3	23.5	40.7	<0.001[e]	28.1	19	0.03[f]
Annualised UPDRS III (UPDRS III/disease duration), (mean ± SD)	11.5 ± 9.7	10.2 ± 7.2	11.5 ± 10.8	13.5 ± 10.7	<0.001	12	10.6	0.33
Observer-independent tests								
Right arm dexterity, Peg board, (mean ± SD)	10.0 ± 2.6	11.1 ± 2.5	9.7 ± 2.5	8.9 ± 2.5	<0.001[e]	9.4 ± 2.4	11 ± 2.6	<0.001[f]
Left arm dexterity, Peg board, (mean ± SD)	9.7 ± 2.5	10.6 ± 2.5	9.5 ± 2.3	8.7 ± 2.4	<0.001[e]	9.3 ± 2.4	10.3 ± 2.5	<0.001[f]
Arm coordination, Peg board, (mean ± SD)	16.8 ± 6.2	19.4 ± 6.6	16.4 ± 5.1	13.3 ± 5.5	<0.001[e]	16 ± 6	18 ± 6.3	<0.001[f]
Arm asymmetry (absolute value of right score - left score), Peg board, (mean ± SD)	0.31 ± 2.53	0.5 ± 2.7	0.2 ± 2.5	0.2 ± 2.4	0.338[e]	0.1 ± 2.5	0.6 ± 2.5	0.027[f]
Get-up-and-go, seconds, (mean ± SD)	10.3 ± 4.3	9.2 ± 4.2	9.9 ± 3.3	12.7 ± 5	<0.001[e]	9.8 ± 3.4	11 ± 5.3	0.001[f]
Flamingo test dichotomised passed, (%)	45.3	66.7	41.4	18.4	<0.001[e]	46	44.2	0.35[f]

[a] Adjusted for age.
[b] Adjusted for gender.
[c] Adjusted for gender and age at diagnosis.
[d] Adjusted for age at diagnosis.
[e] Adjusted for disease duration, gender.
[f] Adjusted for age, disease duration.

Table 3
UPDRS (parts II and IV) and PD medication stratified by age group and gender.

Dependent variable	Total $N = 490$	Age stratification				Gender stratification		
		≤65 $N = 178$	>65, ≤75 $N = 204$	>75 $N = 108$	P for trend	Males $N = 306$	Females $N = 184$	P value
UPDRS II, motor aspects of experience of daily living								
Total UPDRS II, (mean ± SD)	9.4 ± 6.2	9.3 ± 6.3	8.5 ± 5.8	11.2 ± 6.6	0.07[a]	9.8 ± 6.2	8.6 ± 6.2	0.03[b]
Speech problems, (%)	40.4	47.5	34.7	44.9	0.267[a]	47.7	31.3	<0.001[b]
Saliva & drooling, (%)	50.2	49.7	49.3	57	0.23[a]	58.4	39	<0.001[b]
Chewing & swallowing, (%)	22.0	26	16.7	29	0.962[a]	26.2	17	0.02[b]
Eating problems, (%)	45.3	52.5	38.9	49.5	0.363[a]	48.5	42.3	0.12[b]
Dressing problems, (%)	59.0	56.5	58.1	69.2	0.045[a]	63	54.9	0.06[b]
Hygiene, (%)	39.4	43.5	34.5	45.8	0.983[a]	42.6	36.3	0.13[b]
Handwriting problems, (%)	60.4	66.1	54.2	67.3	0.829[a]	67.2	51.6	<0.001[b]
Hobbies, (%)	60.2	61.6	57.6	68.9	0.395[a]	62.6	59.7	0.46[b]
Turning in bed, (%)	52.2	47.7	53.7	62.6	0.014[a]	51.8	56.4	0.38[b]
Tremor, (%)	79.4	81.4	80.8	78.5	0.701[a]	80	81.3	0.80[b]
Getting out of bed, chair, (%)	67.6	58.2	70.9	81.3	<0.001[a]	68.9	68.1	0.83[b]
Walking and balance, (%)	63.1	65.5	58.4	73.8	0.362[a]	63.8	65.4	0.79[b]
Freezing, (%)	16.5	19.2	13.3	21.5	0.935[a]	16.7	18.1	0.86[b]
UPDRS IV, motor complications								
Total UPDRS IV, (mean ± SD)	0.34 ± 1.37	0.6 ± 2	0.2 ± 0.8	0.2 ± 0.6	0.005[a]	0.3 ± 1.4	0.3 ± 1.4	0.63[b]
Presence of Dyskinesia, (%)	5.3	7.3	4.4	3.7	0.138[a]	5.9	4.3	0.29[b]
Presence of Motor Fluctuations, (%)	4.1	6.2	3	3.7	0.242[a]	4.6	3.8	0.42[b]
PD medication								
Total patients on medication, (%)	88.6	87.1	90.2	88.0	0.793[a]	88.2	89.1	0.92[b]
Total LEDD, (mean ± SD)	335 ± 211	264.1 ± 229.5	307.1 ± 232.5	314.2 ± 206	0.046[a]	302.4 ± 221.1	277.5 ± 234.8	0.09[b]
Number on Levodopa, (%)	53.9	28.1	62.3	80.6	<0.001[a]	56.9	48.9	0.07[b]
Number on agonists, (%)	36.1	56.2	32.8	9.3	<0.001[a]	32.4	42.4	0.05[b]
Number on MAO-B inhibitors, (%)	26.9	34.8	28.4	11.1	<0.001[a]	28.8	23.9	0.17[b]
Response to medication, Clinical Global Impression of Change, (%)	81.7	87.9	75.1	84.4	0.262[a]	81.1	82.6	0.74[b]

[a] Adjusted for disease duration, gender.
[b] Adjusted for age, disease duration.

responsiveness was similar by age. There were also marked gender differences for the motor aspects of daily living activities with men reporting more problems with speech, drooling, chewing, swallowing and handwriting and leading to an overall worse total UPDRS-II. Interestingly, women were significantly more likely than men to take dopamine agonists though this result should be viewed with caution.

3.3. Non-motor symptoms

Non-motor features of the two cohorts are summarized in Supplemental Table 3. All indices of cognitive performance were lower in the PD group (MMSE, MOCA, phonemic and semantic fluency). This was also reflected in more patients scoring within the MCI and dementia range. Patients had differing personality profiles (lower extraversion, conscientiousness and openness; higher neuroticism). Depression and anxiety were more common amongst patients (24.5% and 22%), even after controlling for effects of those variables on each other. Other non-motor features with significant differences between patients and controls were: hyposmia, daytime sleepiness, RBD and orthostatic hypotension. Rates of constipation were not different between groups, however use of laxatives was significantly more common in PD. Some non-motor features (sleepiness, hypothension) are modified by medication but that was not explored in our analysis.

Age influenced the presence of non-motor features (Table 4) usually worsening them though in some cases reducing the frequency. Specifically, general health state, cognitive function, use of laxatives, orthostatic hypotension, urinary problems and erectile dysfunction worsened whilst impulse control disorders, anxiety and hallucinations were better in older patients. Further adjustment for agonist use made the effect of age on hallucinations insignificant. Female patients had milder cognitive problems, daytime sleepiness, RBD features, orthostatic hypotension and sexual dysfunction but worse pain scores.

4. Discussion

In order to compare characteristics of our cohort with other large studies we performed a pubmed.com search which yielded 59 publications describing 35 cohorts of PD patients (Supplemental Table 4). Eight of those focused on patients with early stage disease within 4 years of diagnosis/onset (bold highlight). The average age of those patients was slightly lower than in our cohort with the ParkWest [3] cohort being most similar. The gender composition was comparable to our group while the UPDRS-III was considerably lower in other studies.

There are three major features of our study, which set us apart from other published cohorts. Firstly, OPDC cohort is the only one of the early cohorts recruiting a control group, providing a unique opportunity to compare patient characteristics with healthy subjects. Secondly, the breadth of clinical features covered, comparable only to the ParkWest cohort [3], enables us to characterize the disease picture in a lot of detail. Thirdly, our cohort has one of the highest numbers of participants with only the NINDS-PD Long Term Study 1 [4] and the DATATOP study [5] reporting larger number of patients.

5. Age effect

The effect of age on clinical phenotype was suggestive of increased severity in older patients. The performance was worse on motor indices (total UPDRS-III and subscores, H&Y, peg-board, get-up-and-go) and non-motor scales (cognition, anxiety, constipation, urinary and erectile symptoms). Those effects cannot be attributed to medication dose (LEDD increasing with age), responsiveness to medication or disease duration (similar across strata). Later diagnosis in elderly subjects does not play a role either, as evidenced by similar times from symptom onset to diagnosis and to study visit for all age strata. A similar worsening in disease severity has been

Table 4
Non-motor symptoms stratified by age group and gender in PD group.

Dependent variable	Total $N = 490$	Age stratification				Gender stratification		
		≤65 $N = 178$	>65, ≤75 $N = 204$	>75 $N = 108$	P for trend	Males $N = 306$	Females $N = 184$	P value
General health state, EQ-VAS, (mean ± SD)	86.7 ± 10.7	88.2 ± 7.8	87.3 ± 11	83.1 ± 13.3	0.001[a]	87.4 ± 9.6	85.6 ± 12.2	0.09[c]
Total UPDRS I score, Non-motor symptoms, (mean ± SD)	9.0 ± 5.2	9.2 ± 5.8	8.4 ± 4.5	9.8 ± 5.5	0.49[a]	8.8 ± 5	9.4 ± 5.6	0.22[c]
Cognitive measures								
MMSE, (mean ± SD)	27.3 ± 2.6	28 ± 2.1	27.2 ± 2.2	26.5 ± 2.3	<0.001[b]	27.5 ± 2.1	27.1 ± 2.4	0.27[d]
MOCA, (mean ± SD)	24.9 ± 3.5	26.3 ± 2.7	24.7 ± 3.6	23.1 ± 3.4	<0.001[b]	24.5 ± 3.5	25.5 ± 3.4	<0.001[d]
Phonemic Fluency, (mean ± SD)	10.9 ± 3.9	11.6 ± 3.6	10.6 ± 4.3	10.4 ± 3.7	0.07[b]	10.7 ± 4	11.3 ± 3.8	0.02[d]
Semantic Fluency, (mean ± SD)	10.1 ± 3.4	10.7 ± 3.2	10 ± 3.6	9.1 ± 3.1	<0.001[b]	9.6 ± 3.4	10.8 ± 3.3	<0.001[d]
Psychological/psychiatric								
BFI personality traits								
Extraversion, (mean ± SD)	23.8	24.5 ± 6.6	24 ± 6.1	22.1 ± 6.4	0.01[a]	23.4 ± 6.4	24.4 ± 6.3	0.11[c]
Agreeableness, (mean ± SD)	36.8	36.6 ± 5.2	36.6 ± 5.2	37.3 ± 4.9	0.37[a]	36.2 ± 5.3	37.6 ± 4.7	0.004[c]
Conscientiousness, (mean ± SD)	35.8	35.3 ± 5.8	36.3 ± 5.5	35.5 ± 6.1	0.52[a]	35.2 ± 5.9	36.8 ± 5.3	0.004[c]
Neuroticism, (mean ± SD)	22.4	23.1 ± 6.9	22.4 ± 6	21.2 ± 7.3	0.11[a]	21.8 ± 6.7	23.4 ± 6.6	0.01[c]
Openness, (mean ± SD)	34.1	34.7 ± 7.3	34.1 ± 7.2	33 ± 6.8	0.16[a]	34.7 ± 7.3	33.1 ± 6.9	0.02[c]
Depression, Leeds SAD General, (%)	24.5	27.5	20.3	28.3	0.42[a]	22.0	29.1	0.45[c]
Anxiety, Leeds SAA General, (%)	22.0	29.4	19.3	16.2	0.007[a]	18.8	28.3	0.06[c]
Any ICD, QUIP, (%)	9.8	24.3	8.6	5.8	<0.001[g]	14	13.2	0.34[f]
Any other OCD, QUIP, (%)	13.9	26.1	14.1	4.8	<0.001[g]	17.9	14	0.07[f]
Overmedicating, QUIP, (%)	2.3	4.7	1	1	0.05[g]	2.7	1.7	0.49[c]
Fatigue in PD, UPDRS I, (%)	72.8	74.6	67.8	79.4	0.67[a]	72.4	73.6	0.83[c]
Apathy in PD, UPDRS I, (%)	18.2	23.6	14.7	15.7	0.06[a]	17.6	19	0.81[c]
Hallucinations in PD, UPDRS I, (%)	14.7	19.7	13.3	9.3	0.01[a]0.12[g]	15.4	13.6	0.43[c]
Autonomic & other								
BMI, (mean ± SD)	27.4 ± 4.8	27.9 ± 5.4	27.1 ± 4.5	26.9 ± 4.3	0.04[a]	27.5 ± 4.3	27.1 ± 5.6	0.39[c]
Hyposmia, Sniffin Sticks, (%)	74.3	78.6	78	87.1	0.13[a]	82.3	76.7	0.16[c]
Sleepiness, ESS, (%)	24.1	25.8	21.6	27.1	0.99[a]	28.4	17.5	0.004[c]
RBD, RBD-SQ, (%)	43.5	47.5	45	44.7	0.55[a]	49	40.6	0.05[c]
Constipation, (%)	41.0	39.5	42.3	53.4	0.08[a]	41.6	47	0.19[c]
Use of laxatives, (%)	21.8	15.3	24.6	30.8	0.002[a]	23.4	21.2	0.55[c]
Orthostatic hypotension, (%)	23.7	16.9	22.8	38.9	<0.001[a]	28.3	17.4	0.008[c]
Pain in PD, UPDRS I, (%)	52.1	83.6	75.2	85	0.92[a]	77	86.3	0.02[c]
Lightheadedness, UPDRS I, (%)	44.0	44.1	41.1	49.5	0.40[a]	43.4	45.1	0.76[c]
Urinary problems, UPDRS I, (%)	64.4	59.9	63.4	73.8	0.02[a]	64.1	64.8	0.83[c]
Sexual dysfunction, (%)	19.3	18.9	21.4	16	0.70[a]	28.4	4	<0.001[c]
Erectile dysfunction, (%)	42.8	33.7	56.8	68.3	<0.001[e]	**N/A**	**N/A**	

[a] Adjusted for disease duration, gender.
[b] Adjusted for years of education, disease duration, gender.
[c] Adjusted for age, disease duration.
[d] Adjusted for age, years of education, disease duration.
[e] Adjusted for disease duration.
[f] Adjusted for age at onset, gender, disease duration and dopaminergic agonist use.
[g] Adjusted for disease duration, gender, use of dopaminergic agonists.

noted in large studies of late versus early onset PD [6,7]. One possibility is that the overall disease burden in older individuals affected the severity ratings or that natural age-related slowing worsened the picture [8]. However, it is also well known that late-onset PD progresses quicker than early-onset [9], which in our study was reflected in increased annualized UPDRS-III score with age (as proxy for disease progression). On the pathological level, higher clinical progression rate in older subjects may be caused by faster degeneration of dopaminergic terminals [10]. Moreover, the fact that all of the age comparisons in our study survived correction for disease duration provides a firm support for the hypothesis that age is a stronger contributor to PD progression than disease duration [9]. Notably, the only motor feature that bucked this trend was rigidity, which is in agreement with previous work [7].

Interestingly, patient-rated disease severity (UPDRS-II) showed rather moderate changes with age, compared to objective measures (UPDRS-III, Peg-board, Get-up-and-go). This could be a result of a change with age in patients' expectations of their own fitness (older patients expect to be less fit and are more accepting of the disease). A contributing factor could also be a mild level of disease severity in this early cohort. Other features standing out from the overall trend of age-related deterioration were motor complications, ICD's and hallucinations, which all demonstrated decreasing severity with age. Previous studies have shown that dyskinesia and ICD's occur together [11] and that both decrease with age [7]. Hallucinations, on the other hand, may increase with age [12] but they also increase with use of dopaminergic agonists [13]. Taking both those counteracting trends into account, the difference in rate of hallucinations was not significant.

We observed increased levodopa use and decreased use of agonists with age. This effect may be related to greater disease severity requiring stronger treatment but also to avoidance of agonists in older patients for fear of provoking hallucinations [7]. Age in all above analyses emerged as a strong factor despite a relative under-ascertainment of elderly subjects compared to the group initially approached for participation.

6. Gender effect

A complex set of differences emerged from the comparison of gender-related phenotypes. In terms of motor features, a gradient of severity across body areas was identified, whereby men, compared to women, had much more advanced symptoms in the face and neck, with lesser difference in the arms and equal severity

in the legs. In turn, women showed greater severity on postural scores. Importantly, the upper body symptoms differed both on examination and on patient-reported measures while postural/gait problems differed at diagnosis and on examination but not on patient-reported measures.

Most studies agree on increased prevalence of drooling [14,15] and speech problems [14] in men with PD, with more variable reports on swallowing [15,16]. Gender differences in limb symptoms have not been studied, to our knowledge. However, two studies reported increased severity of postural instability in women [17,18] and both showed increased rigidity in men, in agreement with our findings.

The cause for gender-related dissociation of upper body symptoms from gait problems is not clear. Upper body symptoms, in particular rigidity and bradykinesia, are classical manifestations of striato-nigral pathology. Importantly, SPECT studies in healthy women [19,20] and female PD patients [21] show more abundant dopaminergic terminals in the striatum than in men. Hence, we speculate that less severe upper body symptoms in women result from less pathology in the dopaminergic systems. In contrast, postural symptoms are a consequence of cholinergic degeneration in the pedunculo-pontine nucleus but we are not aware of studies investigating gender differences in this region. Alternatively, postural and gait differences between sexes could be unrelated to the disease process. It has been shown, for example, that healthy women have slower walking speed and get-up-and-go test than men [8]. In support of that view, it could be argued that lack of differences on subjective assessment of gait/posture represents true lack of change compared to premorbid condition (women do not think their gait/balance is worse because they generally have poorer balance and walk slower than men). Contrary to that interpretation, however, comparison of get-up-and-go test between genders in our controls did not show any differences (data not presented).

Another gender-related feature was greater symmetricality of symptoms in men. It may seem to contradict the previous finding of women having more postural problems as symmetry of symptoms is generally associated with axial disease. However, these are two separate features, with symmetricality refering to lateralised symptoms only and disregarding axial symptoms. Two other studies showed non-significantly increased symmetricality in men [22,23] although others did not find a gender effect [24]. As with the upper/lower body gradient, a cause for this phenomenon is unclear but we speculate that it may be related to greater symptom severity in men. It is widely accepted that symptoms become more symmetrical with disease progression [24]. Since in our sample men had more severe symptoms in upper limbs we can assume that the disease process was more advanced in men and, hence, greater percentage of men reached symmetrical disease stage. It is also possible that men have more symmetrical striatonigral pathology but there are no pathological or imaging studies of this problem in the literature.

Gender showed multiple significant effects on the non-motor features. In agreement with previous studies, men had more pronounced cognitive impairment as measured by MOCA and fluency tests [25], more daytime sleepiness [26] and more RBD-related features [27]. Cognitive impairment in PD has been shown to co-occur with RBD [28]. Some longitudinal studies reported quicker cognitive decline in RBD [29] and, importantly, in PD with RBD [30]. In view of the strong correlation of gender with both RBD and cognitive decline in our study, it would be important to investigate whether RBD is an equally strong risk factor for dementia in both sexes.

7. Strengths and limitations

A major limitation of our study is its cross-sectional nature, which may bias some variables through retrospective reporting. However, longitudinal data will gradually become available as patients come to follow-up. Another potential weakness of our analyses is that effects of age and gender were investigated in univariate comparisons. Our goal here was to provide a broad overview of symptoms in the early stage of PD and to identify areas of interest for further study. Hence, more detailed and rigorous analyses will be performed in future publications.

8. Conclusions

Our results confirm that age is a strong predictor of disease severity even after taking into account disease duration. Gender-related motor phenotype can be defined by a vertical split into more symmetrical upper-body disease in men and postural disease in women. Amongst the non-motor symptoms, men are more cognitively impaired and have higher rate of RBD than women. Future research is needed to establish whether the two genders may have different predictive value for disease progression.

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Ethical approval

Berkshire Research Ethics Committee.

Disclosures

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Appendix A. Supplementary data

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