Age at onset and Parkinson disease phenotype

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ABSTRACT

Objective: To explore clinical phenotype and characteristics of Parkinson disease (PD) at different ages at onset in recently diagnosed patients with untreated PD.

Methods: We have analyzed baseline data from the Parkinson's Progression Markers Initiative database. Four hundred twenty-two patients with a diagnosis of PD confirmed by DaTSCAN imaging were divided into 4 groups according to age at onset (onset younger than 50 years, 50–59 years, 60–69 years, and 70 years or older) and investigated for differences in side, type and localization of symptoms, occurrence/severity of motor and nonmotor features, nigrostriatal function, and CSF biomarkers.

Results: Older age at onset was associated with a more severe motor and nonmotor phenotype, a greater dopaminergic dysfunction on DaTSCAN, and reduction of CSF α-synuclein and total tau. The most common presentation was the combination of 2 or 3 motor symptoms (bradykinesia, resting tremor, and rigidity) with rigidity being more common in the young-onset group. In about 80% of the patients with localized onset, the arm was the most affected part of the body, with no difference across subgroups.

Conclusions: Although the presentation of PD symptoms is similar across age subgroups, the severity of motor and nonmotor features, the impairment of striatal binding, and the levels of CSF biomarkers increase with age at onset. The variability of imaging and nonimaging biomarkers in patients with PD at different ages could hamper the results of future clinical trials. *Neurology®* 2016;86:1400–1407

GLOSSARY

$A\beta_{1-42}$ = β-amyloid 1–42; **α-syn** = α-synuclein; **HC** = healthy control; **HVLT** = Hopkins Verbal Learning Test; **H&Y** = Hoehn and Yahr; **MDS-UPDRS** = Movement Disorder Society–Unified Parkinson's Disease Rating Scale; **MoCA** = Montreal Cognitive Assessment; **PD** = Parkinson disease; **PPMI** = Parkinson's Progression Markers Initiative; **p-tau$_{181}$** = tau phosphorylated at Thr181; **SCOPA-AUT** = Scales for Outcomes in Parkinson's Disease–Autonomic; **STAI** = State-Trait Anxiety Inventory; **t-tau** = total tau; **UPSIT** = University of Pennsylvania Smell Identification Test.

Parkinson disease (PD) is heterogeneous in clinical manifestations[1] and progression.[2] The biological basis of this phenotypic variability is unknown but might be explained by the progressive and diverse accumulation of α-synuclein (α-syn) in different brain structures.[3,4] It has been estimated that PD increases with age, reaching a prevalence of 2.6% in people aged 85 to 89 years.[5] Although current evidence does not support the hypothesis that PD is caused by an acceleration of a natural aging process,[6] age is considered its main risk factor.[7] Lewy body pathology is related to age[8] and, in the general population, the occurrence of mild extrapyramidal signs increases with age.[8] These observations implicate a role for age in the progressive decline of nigrostriatal function.[9] However, evidence supporting an influence of age on PD phenotype at its onset is lacking and conflicting.[10–18] Previous studies have poorly assessed the full spectrum of motor and nonmotor symptoms and they have not evaluated the relationship between PD phenotype and imaging and nonimaging biomarkers.

Supplemental data
at Neurology.org

The Parkinson's Progression Markers Initiative (PPMI) is an ongoing, international, multicenter, prospective study designed to discover and validate biomarkers of disease progression in newly diagnosed, drug-naive patients with PD. Here, we have analyzed baseline data from the PPMI database to explore the characteristics of patients with PD at different ages at onset.

METHODS **Population.** Demographic information, clinical characteristics, and results of clinical and biochemical tests were downloaded on August 13, 2014, from the PPMI database.[19] Inclusion criteria were age 30 years or older, diagnosis of PD (based on one of the following: presence of [1] asymmetrical resting tremor or [2] asymmetrical bradykinesia or [3] at least 2 of resting tremor, bradykinesia, and rigidity), disease duration of 1 to 24 months, Hoehn and Yahr (H&Y) stage of 1 to 2, and presence of striatal dopamine transporter deficit on ^{123}I-ioflupane SPECT imaging (DaTSCAN).

None of the patients was on antiparkinsonian medications or monoamine oxidase inhibitor inhibitors.

At enrollment, participants were assessed for clinical features and underwent DaTSCAN imaging. CSF and serum samples were collected. Healthy controls (HCs) were recruited if free of current or active neurologic disorder and had normal DaTSCAN. Details about assessments and analyses are described in the e-Methods on the *Neurology*® Web site at Neurology.org.

Our PD population was divided into subgroups according to the decade of their age at symptomatic onset (younger than 50 years, 50–59 years, 60–69 years, and 70 years or older). Age-related differences in clinical phenotype and imaging and nonimaging biomarkers were evaluated. This age-subgroup classification was chosen following a cluster analysis of patients with early PD.[20] Age at onset was based on patients' recollection of first symptoms.

Standard protocol approvals, registrations, and patient consents. The PPMI study is registered with ClinicalTrials.gov (NCT01141023). Each PPMI site received approval from an ethical committee on human experimentation before study initiation. Written informed consent for research was obtained from all individuals participating in the study.

Statistical analysis. Continuous variables were expressed as mean ± SD and compared across subgroups with analysis of variance if normally distributed and with the Kruskal-Wallis correction when not normally distributed. Normality of data distribution was interrogated using the Kolmogorov-Smirnov test. Significance of multiple comparisons was assessed after performing a Bonferroni correction. Categorical variables were expressed as proportions and compared using a χ^2 test. Correlations were interrogated using Spearman rank correlation. Data were collected and analyzed using SPSS version 19.0 (IBM Corp., Armonk, NY). Statistical significance was accepted at $p < 0.05$.

RESULTS **Patient characteristics.** Table 1 shows demographic and clinical characteristics of the PD population. We studied 422 patients with PD, 276 male (65.4%), with a mean age of 61.6 ± 9.7 years and mean years of education of 15.5 ± 3.0. Three hundred seventy-five patients (88.8%) were right-handed,

Table 1	Characteristics of all patients with PD and at different ages at onset					
		Age at onset, y				
	All (n = 422)	<50 (n = 58)	50–59 (n = 117)	60–69 (n = 168)	≥70 (n = 79)	p Value
Age, y, mean ± SD	61.6 ± 9.73	45.03 ± 4.97	55.74 ± 2.92	65.46 ± 2.99	74.25 ± 3.3	—
Sex, male, % (n)	65.4 (276)	63.8 (37)	55.6 (65)	71.4 (120)	68.4 (54)	—
PD duration, mo, mean ± SD	6.58 ± 6.51	6.78 ± 7.15	6.49 ± 6.59	6.43 ± 6.09	6.86 ± 6.88	1.000
H&Y stage, mean ± SD	1.56 ± 0.51	1.40 ± 0.49	1.49 ± 0.52	1.61 ± 0.50[a]	1.70 ± 0.46[a,b]	0.001
Family history of PD, % (n)	24.2 (102)	25.9 (15)	26.5 (31)	22.0 (37)	24.1 (19)	0.835
Years of education, mean ± SD	15.54 ± 2.99	15.79 ± 2.62	15.28 ± 2.62	15.49 ± 3.10	15.84 ± 3.50	0.413
Motor subtype, % (n)						0.533
Tremor-dominant	17.8 (75)	20.7 (12)	14.5 (17)	16.1 (27)	24.1 (19)	
Akinetic-dominant	78 (329)	75.9 (44)	81.2 (95)	80.4 (135)	69.6 (55)	
Mixed	4.3 (18)	3.4 (2)	4.3 (5)	3.6 (6)	6.3 (5)	
MDS-UPDRS, mean ± SD						
Part I	5.57 ± 4.07	5.21 ± 4.12	5.38 ± 3.72	5.68 ± 4.48	5.86 ± 3.60	0.516
Part II	5.90 ± 4.20	6.09 ± 5.03	5.20 ± 3.52	6.04 ± 4.32	6.53 ± 4.10	0.181
Part III in OFF	20.89 ± 8.87	18.09 ± 7.97	19.80 ± 8.47	21.49 ± 8.81[a]	23.30 ± 9.55[a]	0.005
Total	32.35 ± 13.15	28.38 ± 14.16	30.38 ± 11.44	33.21 ± 13.73	35.64 ± 12.81[a]	0.009

Abbreviations: H&Y = Hoehn and Yahr; MDS-UPDRS = Movement Disorder Society–Unified Parkinson's Disease Rating Scale; PD = Parkinson disease. Bonferroni analysis performed.
[a] p Value < 0.05 vs age at onset <50 years.
[b] p Value < 0.05 vs age at onset 50-59 years.

76 patients (8.8%) were left-handed, and 10 patients (2.4%) were ambidextrous. One hundred two patients (24.2%) had a family history of PD. Mean PD duration was 6.6 ± 6.5 months. Mean H&Y stage was 1.56 ± 0.51 and Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total mean score was 32.4 ± 13.2. Fifty-eight patients had age at onset younger than 50 years, 117 had age at onset between 50 and 59 years, 168 between 60 and 69 years, and 79 had age at onset of 70 years or older. There were no differences for years of education, family history of PD, and PD duration. Table e-1 shows characteristics of the control population.

Side predominantly affected at onset. Disease onset was asymmetrical in 403 patients (97.8%) and symmetrical in 9 (2.2%). In patients with asymmetrical onset, 234 (56.8%) had the dominant side predominantly affected and 169 (41%) the nondominant side. In subgroups with older age at onset, the number of patients with the dominant side more affected and symmetrical onset was higher compared to younger subgroups ($p = 0.002$) (table 2).

Localization of motor symptoms. MDS-UPDRS III subitems were analyzed to identify involvement of specific parts of the body. In 191 patients (45.3%), the disease predominantly affected a specific part of the body (head-predominant, arm-predominant, or leg-predominant; see e-Methods for details about this classification). Of these patients, 162 (85%) had arm-predominant symptoms, 15 (8%) had head-predominant symptoms, and 14 (7.3%) had leg-predominant symptoms. Most patients had arm-predominant symptoms (80%–86%) (table 2).

Symptoms at time of diagnosis. Fifty-two patients (12.4%) reported only one motor symptom (resting tremor [40 patients, 76.9%], bradykinesia [10 patients, 19.2%], or rigidity [2 patients, 3.8%]), 151 (35.9%) reported 2 motor symptoms, 200 (47.5%) reported 3 motor symptoms, and 18 (4.3%) reported all 4 motor symptoms of PD (table 3). Overall the percentage of patients with 1, 2, 3, and 4 motor symptoms at time of diagnosis was similar across age subgroups ($p = 0.5$). In the subgroup with age at onset younger than 50 years, 94.5% (n = 54) of the patients reported rigidity and this rate was higher compared to other age-at-onset subgroups ($p = 0.003$). The percentages of patients reporting bradykinesia, resting tremor, and postural instability rate were similar at different ages at onset ($p = 0.626$, $p = 0.130$, and $p = 0.839$, respectively) (table 3).

Motor features. Table 1 shows details of motor features. The mean H&Y stage for the whole cohort of patients was 1.56 ± 0.51. They had an MDS-UPDRS Part II mean score of 5.9 ± 4.20 and an MDS-UPDRS Part III motor mean score of 20.9 ± 8.9. Seventy-five patients (17.8%) showed a tremor-dominant subtype, 329 (78%) an akinetic-rigid subtype, and 18 (4.3%) a mixed subtype. Details regarding definition of motor subtypes are provided in the e-Methods. MDS-UPDRS subscore for bradykinesia was 10.41 ± 5.68 (range 0–52), 3.79 ± 2.65 for rigidity (range 0–20), 2.79 ± 2.42 for resting tremor (range 0–24), and 0.68 ± 0.73 for postural instability (range 0–12) (table 3).

H&Y stage and MDS-UPDRS III score was higher in the subgroups with older age at onset ($p = 0.001$ and $p = 0.005$, respectively). However, no differences were found for MDS-UPDRS Part II and motor subtypes ($p = 0.181$ and $p = 0.533$, respectively) (table 1). Bradykinesia, resting tremor, and postural instability scores were more severe in the subgroup with older age at onset than in the younger subgroups ($p = 0.040$, $p = 0.004$, and $p = 0.039$, respectively),

Table 2	Predominantly affected side and localization of motor symptoms in all patients with Parkinson disease and at different ages at onset					
		Age at onset, y				
	All	**<50**	**50-59**	**60-69**	**≥70**	**p Value**
Predominantly affected side	n = 412	n = 57	n = 113	n = 164	n = 78	
Nondominant side	41 (169)	54.4 (31)	45.1 (51)	36.6 (60)	34.6 (27)	0.002
Dominant side	56.8 (234)	45.6 (26)	54.9 (62)	61.6 (101)	57.7 (45)	
Symmetrical involvement	2.2 (9)	0 (0)	0 (0)	1.8 (3)	7.7 (6)	
Localization of motor symptoms	n = 191	n = 30	n = 52	n = 74	n = 35	
Head-predominant	7.9 (15)	0 (0)	3.8 (2)	9.5 (7)	17.1 (6)	0.530
Arm-predominant	84.8 (162)	86.7 (26)	84.6 (44)	86.5 (64)	80 (28)	
Leg-predominant	7.3 (14)	13.3 (4)	11.5 (6)	4.1 (3)	2.9 (1)	

Data represent % (n).

Table 3   Number, rate, and severity of motor signs at different ages at onset

		Age at onset, y				
	All	<50	50–59	60–69	≥70	p Value
No. of motor signs	n = 421	n = 58	n = 117	n = 168	n = 78	
1	12.4 (52)	3.4 (2)	13.7 (16)	12.5 (21)	16.7 (13)	0.500
2	35.9 (151)	36.2 (21)	36.8 (43)	35.7 (60)	34.6 (27)	
3	47.5 (200)	58.6 (34)	44.4 (52)	47.6 (80)	43.6 (34)	
4	4.3 (18)	1.7 (1)	5.1 (6)	4.2 (7)	5.1 (4)	
Rate of motor signs	n = 422	n = 58	n = 117	n = 168	n = 79	
Bradykinesia	82.2 (347)	86.2 (50)	84.5 (98)	82.5 (137)	78.5 (62)	0.626
Rigidity	75.8 (320)	94.8 (55)	76.1 (89)[a]	73.1 (122)[a]	70.1 (54)[a]	0.003
Tremor	78.2 (330)	72.4 (42)	72.6 (85)	82.7 (139)	81.0 (64)	0.130
Postural instability	6.9 (29)	5.4 (3)	8.7 (10)	6.6 (11)	6.3 (5)	0.839
Severity of motor signs, MDS-UPDRS subscore	n = 422	n = 58	n = 117	n = 168	n = 79	
Bradykinesia (0–52)	10.41 ± 5.68	8.91 ± 5.06	10.00 ± 5.35	10.66 ± 5.64	11.57 ± 6.42[a]	0.040
Rigidity (0–20)	3.79 ± 2.65	3.76 ± 2.64	3.77 ± 2.67	3.87 ± 2.65	3.68 ± 2.67	0.962
Resting tremor (0–24)	2.79 ± 2.42	2.21 ± 2.40	2.26 ± 2.16	2.95 ± 2.50	3.66 ± 2.35[a,b]	0.004
Postural instability (0–12)	0.68 ± 0.73	0.45 ± 0.63	0.66 ± 0.76	0.73 ± 0.75	0.78 ± 0.67[a]	0.039

Data represent % (n) or mean ± SD. Bonferroni analysis performed.

[a] p Value < 0.05 vs age at onset <50 years.

[b] p Value < 0.05 vs age at onset 50–59 years.

whereas severity of rigidity was not different across age subgroups ($p = 0.962$) (table 3).

Nonmotor features. Table 4 shows details of nonmotor symptoms analysis. The global nonmotor burden as measured by the MDS-UPDRS Part I was similar among the 4 subgroups ($p = 0.516$) (table 1). However, when rated with specific scales, patients with an older age at onset showed a greater impairment of autonomic (Scales for Outcomes in Parkinson's Disease–Autonomic [SCOPA-AUT], $p < 0.0001$), olfactory (University of Pennsylvania Smell Identification Test [UPSIT], $p < 0.0001$), and cognitive function (Montreal Cognitive Assessment [MoCA], $p < 0.0001$; Benton Judgment of Line Orientation Score, $p = 0.018$; Hopkins Verbal Learning Test [HVLT] Delayed Recognition False Alarms, $p = 0.032$; HVLT Delayed Recognition Hits, $p = 0.001$; HVLT Immediate Recall, $p < 0.0001$; Semantic Fluency Test score, $p < 0.0001$; Symbol Digit Modalities Test score, $p < 0.0001$). Likewise, the number of patients with impaired autonomic, olfactory, and cognitive functions was higher in the subgroups with older age at onset ($p < 0.0001$, for SCOPA-AUT, $p < 0.0001$ for UPSIT, and $p < 0.0001$ for MoCA, respectively; data not shown). No differences were found in terms of severity of disability (activities of daily living, $p = 0.489$), depression (Geriatric Depression Scale, $p = 0.890$), anxiety (State-Trait Anxiety

Inventory [STAI] total, $p = 0.639$; STAI state subscore, $p = 0.948$; STAI anxiety subscore, $p = 0.486$), impulsive control disorders (Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease score, $p = 0.673$), and sleep problems (Epworth Sleepiness Scale, $p = 0.980$; REM Sleep Behavior Disorder Screening Questionnaire, $p = 0.941$).

Striatal binding of ^{123}I-ioflupane (DaTSCAN). Table 5 shows DaTSCAN findings. Data are presented as reduction in ^{123}I-ioflupane binding compared to the mean of the HCs (see details in e-Methods). In all patients, striatal uptake of ^{123}I-ioflupane was asymmetrical with one side more affected than the other. In each patient, we identify the caudate and putamen with the largest reduction of ^{123}I-ioflupane binding (referred to below as the most affected caudate and most affected putamen). The contralateral striatal nuclei were defined as the least affected caudate and putamen. Each nucleus was considered abnormally reduced when reduction was greater than 2 SDs below mean value of HCs for that region. Across the whole population of patients, the mean percentage reduction in ^{123}I-ioflupane binding was 68.5% ± 12.4% for the most affected putamen, 53.8% ± 17.4% for the least affected putamen, 39% ± 18.2% for the most affected caudate, and 26.6% ± 20.1% for the least affected caudate. Three hundred ninety patients had an abnormal most affected putamen

Table 4 Nonmotor features at different ages at onset

	All (n = 422)	Age at onset, y				p Value
		<50 (n = 58)	50–59 (n = 117)	60–69 (n = 168)	≥70 (n = 79)	
Autonomic dysfunction						
SCOPA-AUT	9.49 ± 6.16	6.98 ± 5.24	8.77 ± 5.58	10.13 ± 6.31[a]	11.05 ± 6.67[a]	<0.0001
Neurobehavioral impairments						
GDS	2.34 ± 2.45	2.66 ± 2.78	2.38 ± 2.61	2.29 ± 2.46	2.13 ± 1.88	0.890
QUIP score	0.28 ± 0.63	0.31 ± 0.57	0.26 ± 0.65	0.65 ± 0.28	0.67 ± 0.28	0.673
STAI total score	88.16 ± 8.81	87.47 ± 8.64	88.03 ± 9.19	88.16 ± 9.12	88.90 ± 7.71	0.639
STAI state subscore	42.76 ± 4.92	42.40 ± 5.31	42.38 ± 5.23	42.91 ± 5.07	42.81 ± 3.70	0.948
STAI anxiety subscore	45.41 ± 5.24	45.07 ± 5.22	45.34 ± 5.56	45.21 ± 5.14	46.19 ± 4.96	0.486
Neuropsychological impairments						
MoCA	27.29 ± 2.31	28.19 ± 2.40	27.52 ± 2.05	27.04 ± 2.24[a]	26.81 ± 2.56[a]	<0.0001
BJLOS	12.78 ± 2.12	13.22 ± 1.86	12.94 ± 1.90	12.82 ± 2.21	12.13 ± 2.32[a]	0.018
HVLT Delayed Recognition False Alarms	1.24 ± 1.32	0.97 ± 1.17	1.13 ± 1.23	1.46 ± 1.43	1.13 ± 1.23	0.032
HVLT Delayed Recognition Hits	11.18 ± 1.23	11.52 ± 0.73	11.47 ± 0.78	11.01 ± 1.40[a,b]	10.86 ± 1.52[b]	0.001
HVLT Immediate Recall	24.44 ± 4.98	27.12 ± 3.80	25.78 ± 4.75	23.21 ± 4.74[a,b]	23.13 ± 5.37[a,b]	<0.0001
SFT score	48.68 ± 11.64	52.19 ± 10.49	53.09 ± 11.49	46.52 ± 11.26[a,b]	44.24 ± 10.75[a,b]	<0.0001
SDMT score	41.20 ± 9.73	48.81 ± 8.18	44.05 ± 8.13[a]	39.68 ± 9.13[a,b]	34.66 ± 9.01[a,b,c]	<0.0001
LNSR score	14.46 ± 2.04	15.36 ± 1.80	14.68 ± 2.14	13.62 ± 2.02	13.80 ± 1.64	0.162
Olfactory dysfunction						
UPSIT	22.36 ± 8.24	26.33 ± 7.44	24.44 ± 8.03	21.28 ± 7.95[a,b]	18.68 ± 7.77[a,b]	<0.0001
Sleep problems						
ESS	5.76 ± 3.42	5.60 ± 3.32	5.68 ± 3.35	5.88 ± 3.64	5.74 ± 3.13	0.980
RBDSQ	4.5 ± 2.87	4.48 ± 2.72	4.46 ± 2.96	4.60 ± 2.89	4.35 ± 2.85	0.941
Disability						
Modified Schwab and England ADL	93.15 ± 5.87	92.59 ± 5.56	93.59 ± 5.87	92.83 ± 6.13	93.58 ± 5.55	0.489

Abbreviations: ADL = activities of daily living; BJLOS = Benton Judgment of Line Orientation Score; ESS = Epworth Sleepiness Scale; GDS = Geriatric Depression Scale; HVLT = Hopkins Verbal Learning Test; LNSR = Letter Number Sequencing Raw; MoCA = Montreal Cognitive Assessment; QUIP = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; RBDSQ = REM Sleep Behavior Disorder Screening Questionnaire; SCOPA-AUT = Scales for Outcomes in Parkinson's Disease–Autonomic; SDMT = Symbol Digit Modalities Test; SFT = Semantic Fluency Test; STAI = State-Trait Anxiety Inventory; UPSIT = University of Pennsylvania Smell Identification Test.
Data represent mean ± SD. Bonferroni analysis performed.
[a] p Value < 0.05 vs age at onset <50 years.
[b] p Value < 0.05 vs age at onset 50-59 years.
[c] p Value < 0.05 vs age at onset 60-69 years.

(93.5%), 262 patients an abnormal least affected putamen (62.5%), 197 patients had an abnormal most affected caudate (47%), and 93 patients had an abnormal least affected caudate (22.2%) (table 5). Percentage reductions in ^{123}I-ioflupane binding for the most affected putamen were similar across age subgroups ($p = 0.926$) as were the number of patients with abnormal reductions ($p = 0.123$). For the most affected caudate, ^{123}I-ioflupane binding was lower in older age subgroups ($p = 0.048$); however, the number of patients with abnormal caudate reduction was similar across the age subgroups ($p = 0.229$). In the least affected putamen and caudate, ^{123}I-ioflupane binding was lower in older compared with younger subgroups ($p = 0.006$ for putamen and $p = 0.0003$ for caudate)

and the number of patients with abnormal tracer uptake in these regions was higher in older subgroups ($p = 0.004$ for putamen and $p = 0.047$ for caudate) (table 5).

CSF and serum biomarkers. Table e-2 shows characteristics of CSF and serum biomarkers. Across the whole population, the levels of CSF α-syn, total tau (t-tau), and tau phosphorylated at Thr181 (p-tau$_{181}$) were reduced in the patients compared with HCs, while levels of CSF β-amyloid 1–42 (Aβ$_{1–42}$) and serum urate were not different between groups (table e-2). In HCs, all biomarkers increased with the age (Spearman correlation [ρ] = 0.159, $p = 0.029$ for α-syn; ρ = 0.354, $p = 0.030$ for t-tau; ρ = 0.158, $p = 0.030$

Table 5 DaTSCAN at different ages at onset

	All (n = 422)	Age at onset, y				p Value
		<50 (n = 58)	50–59 (n = 117)	60–69 (n = 168)	≥70 (n = 79)	
% Reduction most affected putamen	68.5 ± 12.4	68.7 ± 9.3	69.1 ± 10.7	68.3 ± 14.1	68 ± 12.8	0.926
% Reduction least affected putamen	53.8 ± 17.4	47.1 ± 17.8	53.6 ± 17.1	54.4 ± 18.4[a]	57.6 ± 14.2[a]	0.006
% Reduction most affected caudate	39 ± 18.2	33.4 ± 19.9	38.1 ± 16.3	40.3 ± 18.6	41.5 ± 18.3[a]	0.048
% Reduction least affected caudate	26.6 ± 20.1	17.2 ± 20.8	25.5 ± 19.1	28.6 ± 20.3[a]	31 ± 18.5[a]	0.0003
Patients with abnormal DaTSCAN, % (n)						
Abnormal most affected putamen	93.1 (390)	98.2 (56)	94.9 (111)	92.2 (154)	88.5 (69)	0.123
Abnormal least affected putamen	62.5 (262)	42.1 (24)	62.4 (73)	65.9 (110)[a]	70.5 (55)[a]	0.004
Abnormal most affected caudate	47 (197)	35.1 (20)	46.2 (54)	49.7 (83)	51.3 (40)	0.229
Abnormal least affected caudate	22.2 (93)	10.5 (6)	18.8 (22)	26.3 (44)	26.9 (21)[a]	0.047

[a] Bonferroni analysis: p value < 0.05 vs age at onset <50 years.

for p-tau$_{181}$; and $\rho = 0.182$, $p = 0.008$ for serum urate) except for Aβ$_{1-42}$ ($\rho = -0.012$, $p = 0.871$). In patients with PD, only α-syn ($\rho = 0.124$, $p = 0.012$) and t-tau ($\rho = 0.269$, $p < 0.0001$) increased with the age but not p-tau$_{181}$ ($\rho = 0.054$, $p = 0.277$), Aβ$_{1-42}$ ($\rho = 0.159$, $p = 0.029$), or serum urate ($\rho = 0.068$, $p = 0.166$). In older age subgroups, the reduction (from HCs) of α-syn and t-tau were greater compared with younger age subgroups (table e-2 and figure e-1).

DISCUSSION The main strength of this study is that the clinical features of PD were evaluated in a large population of untreated newly diagnosed patients with a prospective design and a simultaneous evaluation of imaging and nonimaging biomarkers.

We found that older age at onset was associated with a more severe motor and nonmotor PD phenotype, a greater impairment of dopaminergic function on DaTSCAN, and a greater reduction of CSF α-syn and t-tau levels. With the exception of rigidity, which was similar across age groups, the severity of motor impairment (H&Y stage, MDS-UPDRS total and Part III scores, bradykinesia, resting tremor, and postural instability scores) was greater in the oldest age subgroup (70 years or older) compared with younger subgroups. In addition, the number of patients with symmetrical disease at onset was higher in the oldest (70 years or older) compared with younger age subgroups suggesting a more widespread degeneration. Similarly, the oldest age subgroups also presented more severe nonmotor symptoms (autonomic, olfactory, and cognitive dysfunctions) and greater reduction of striatal ^{123}I-ioflupane binding on DaTSCAN compared with younger subgroups. Of note, while ^{123}I-ioflupane uptake in the most affected putamen was similar across the age subgroups, uptake in the most affected caudate, least affected putamen, and least affected caudate was lower in older compared with younger subgroups,

suggesting a more widespread involvement of striatal structures in elderly patients.

Finally, levels of CSF α-syn and t-tau were reduced in patients with PD, as previously suggested in the preliminary analysis of the PPMI population,[21] and this reduction was greater in older age subgroups compared with younger age subgroups. A greater reduction in CSF α-syn and t-tau in patients with older onset could be explained by a higher accumulation of these proteins in the neurons.

Considering that these patients had similar disease duration, our findings of a more severe phenotype and more widespread involvement of striatal structures in the older patients could be attributable to superimposition of PD pathology on the natural aging process. A direct contribution of the aging process to the progressive neurodegeneration of PD or a decrease of compensatory mechanisms in older patients could also have occurred.

Moreover, our data suggest that the heterogeneity of PD at different ages at onset could be reflected by various impairments of imaging and nonimaging biomarkers. This variability in biomarkers in patients with PD with different ages at onset should be taken in account in future clinical trials to test neuroprotective drugs. The recruitment of patients with homogeneous age at onset will reduce this variability, resulting in an increased statistical power with smaller sample sizes. Follow-up observations of the PPMI population will clarify the role of age at onset on disease progression and whether there is an interaction with these biomarkers.

Recently, there has been a great effort to identify and formally delineate PD subtypes.[22,23] So far, none of the proposed subtype classifications appears sufficiently robust to warrant formal delineation.[22] Our findings suggest that in future classifications, early-onset and late-onset subtypes should also be considered.

The association between handedness and first affected side at onset in PD is still controversial, as some studies have reported an association and others failed to demonstrate it.[24] A recent meta-analysis[24] including 4,405 patients with asymmetrical PD has shown that in about 60% of patients, the disease started on the dominant side. This finding is confirmed in the overall population of our study, where the disease was mostly asymmetrical and the dominant side was predominantly affected. However, in the youngest subgroup (younger than 50 years), it was the nondominant side that was mostly affected. It has been suggested that increased movement complexity in the dominant hand could be a risk factor for dopamine cell loss in the contralateral hemisphere via glutaminergic excitotoxicity.[24] Therefore, the dominant hemisphere could be more vulnerable to dopaminergic denervation than the nondominant hemisphere in patients with PD.[25] However, this theory does not explain the onset in the nondominant side in our younger patients and the symmetrical involvement in some of our older patients. Further studies are required to understand the pathophysiologic mechanisms of asymmetry in PD.

The limited data available in the literature indicate that abnormalities of the arm are first noticed in the majority (65%–80%) of patients.[26,27] Similarly, in about 80% of our patients with localized onset, the arm was the most affected part of the body, with no difference across age subgroups. This is in line with our recent [^{18}F]-dopa PET study,[28] which has shown that the middle strip (intermediate) of the putamen was more affected than other striatal subregions in patients with early PD and correlated with severity of arm impairment.

Regarding the motor picture at onset, we did not find any specific feature of PD that was typical of any age subgroup, with the exception of rigidity, which was more commonly noticed by the group with youngest age at onset, as also reported previously.[17,18] Most patients had a combination of 2 or more motor symptoms and we found a similar rate of tremor-predominant and akinetic-rigid patients across age-at-onset subgroups, as also indicated previously.[12]

There are some potential limitations in this study that require further discussion. In older patients, the initial symptoms could have been detected later than in younger patients since these symptoms could be attributed to physiologic aging rather than to a pathologic process. Thus, the disease duration in older patients could be underestimated in comparison with younger patients. However, it should be noticed that the magnitude of tracer uptake in the most affected putamen on DaTSCAN was similar across the age subgroups, suggesting that disease duration was indeed similar in the different subgroups.

Older people have a larger number of comorbidities and medications than younger patients, which might lead to higher scores on clinical scales, particularly for nonmotor symptoms. This is alleviated by the fact that comparison was made with HCs rigorously age- and sex-matched to the PD cohort. Unfortunately, the PPMI study has not included any measure of comorbidities to be used as covariate in comparisons of age subgroups. We strongly suggest that measurements of comorbidities such as the Elixhauser Index or the Romano adaptation of the Charlson Index be added to the PPMI study and to similar database studies in the future.[29]

Finally, about 25% of our patients had a family history of PD and it is possible that some of them were carriers of a genetic mutation. Many genetic forms have an influence on PD phenotype and therefore the presence of patients with genetic forms of PD could be a possible confounding factor in our study. However, this concern is probably mitigated by the equal distribution of family history across all age groups. In addition, genetic forms of PD associated with more severe phenotypes (including more severe and symmetrical striatal loss of dopamine transporter on DaTSCAN) have early onset, affecting young patients; therefore, the possible presence of such patients in our cohort would not change the meaningfulness of our findings.

Comment:
Biomarkers for the progression of Parkinson disease

The chief outlay for a study of the progression of Parkinson disease (PD) is time, and many of the important scientific returns from the Parkinson's Progression Markers Initiative database lie in the future. Pagano et al.[1] have conducted a cross-sectional survey of the de novo PD patient cohort. One of their conclusions is that older patients have greater motor and nonmotor deficits with more widespread striatal dopaminergic lesions on DaTSCAN, implying that longitudinal data should tell us more about the ways that α-synuclein and other pathologies in PD are governed by age.

The task of correlating clinical scale statistics with prospective biomarkers is not straightforward. PD may not be divisible into subtypes beyond general trends of tremor or bradykinesia predominance, and temporal differences between younger and older onset. "Nonmotor symptoms" is useful shorthand for a group of parkinsonian disabilities, but there is no common correspondence with disease stage or pathologic findings among them.

Comparing untreated parkinsonian motor disability with the baseline candidate biomarker testing is potentially valuable. Henceforth, though, clinical observations on this cohort will record motor function that has been modified by pharmacologic therapy. One motivation for the search for biomarkers of PD progression was the unsatisfactory outcome of several clinical trials that had been designed to look for disease-modifying effects. Motor scores could not reliably discern the rate of disease progression from variations in symptomatic treatment. Future assessments should account for the responses to dopaminergic drugs so that the trajectory of the underlying motor progression, which runs at around 2% of the maximum score per year, can be accurately calculated. Otherwise, the same blurring of interpretation of motor scores that hindered previous drug trials will reduce the precision of the correlations with clinical course that are needed to validate the biomarkers.

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