ORIGINAL ARTICLE

Clinical Study of 668 Indian Subjects with Juvenile, Young, and Early Onset Parkinson's Disease

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ABSTRACT: ***Objective:*** To determine the demographic pattern of juvenile-onset parkinsonism (JP, <20 years), young-onset (YOPD, 20–40 years), and early onset (EOPD, 40–50 years) Parkinson's disease (PD) in India. ***Materials and Methods:*** We conducted a 2-year, pan-India, multicenter collaborative study to analyze clinical patterns of JP, YOPD, and EOPD. All patients under follow-up of movement disorders specialists and meeting United Kingdom (UK) Brain Bank criteria for PD were included. ***Results:*** A total of 668 subjects (M:F 455:213) were recruited with a mean age at onset of 38.7 ± 8.1 years. The mean duration of symptoms at the time of study was 8 ± 6 years. Fifteen percent had a family history of PD and 13% had consanguinity. JP had the highest consanguinity rate (53%). YOPD and JP cases had a higher prevalence of consanguinity, dystonia, and gait and balance issues compared to those with EOPD. In relation to nonmotor symptoms, panic attacks and depression were more common in YOPD and sleep-related issues more common in EOPD subjects. Overall, dyskinesias were documented in 32.8%. YOPD subjects had a higher frequency of dyskinesia than EOPD subjects (39.9% vs. 25.5%), but they were first noted later in the disease course (5.7 vs. 4.4 years). ***Conclusion:*** This large cohort shows differing clinical patterns in JP, YOPD, and EOPD cases. We propose that cutoffs of <20, <40, and <50 years should preferably be used to define JP, YOPD, and EOPD.

RÉSUMÉ : Étude clinique de 668 patients indiens atteints de la maladie de Parkinson au moment de l'enfance et de l'adolescence, à un jeune âge et à un âge adulte précoce. ***Objectif :*** Déterminer le profil démographique de patients indiens chez qui la maladie de Parkinson (MP) est apparue au moment de l'enfance et de l'adolescence (MPEA, < 20 ans), à un jeune âge (MPJA, 20-40 ans) et à un âge adulte précoce (MPAAP, 40-50 ans). ***Matériel et méthodes :*** Pendant deux ans, nous avons ainsi mené dans plusieurs établissements de santé une étude panindienne collaborative afin d'analyser les signes cliniques particuliers de patients MPEA, MPJA et MPAAP. À noter que tous les patients suivis par des spécialistes des troubles du mouvement et satisfaisant aux critères de la *United Kingdom Brain Bank* pour la MP ont été inclus dans cette étude. ***Résultats :*** Au total, 668 patients, dont 213 étaient des femmes, ont été recrutés dans le cadre de cette étude, leur âge moyen au moment de l'apparition des premiers symptômes de MP étant de 38,7 ± 8,1 ans. La durée moyenne des symptômes au moment de cette étude avait été de 8 ± 6 ans. Parmi tous ces patients, 15 % avaient des antécédents familiaux de MP alors que 13% donnaient à voir des antécédents de consanguinité. Les patients MPEA sont ceux dont le taux de consanguinité était le plus élevé (53 %). Dans les faits, les patients MPEA et MPJA ont montré une prévalence de consanguinité, de dystonie, de problèmes de la démarche et de l'équilibre plus élevée si on les compare aux patients MPAAP. En ce qui concerne maintenant des symptômes non-moteurs, les crises de panique et la dépression se sont avérées plus courantes chez les patients MPJA alors que des problèmes liés au sommeil l'ont été chez les patients MPAAP. Enfin, des dyskinésies ont été signalées de façon générale chez 32,8 % des patients. À cet égard, les patients MPJA ont montré une fréquence plus élevée de tels troubles si on les compare aux patients MPAAP (39,9 % contre 25,5 %). Cela dit, ils ont été diagnostiqués pour la toute première fois plus tard dans l'évolution de la maladie (5,7 contre 4,4 ans). ***Conclusion :*** Cette cohorte importante montre ainsi des signes cliniques particuliers qui diffèrent selon les catégories d'âge des patients. À cet égard, nous proposons que les seuils d'âge suivants (< 20, < 40 et < 50 ans) soient préférablement utilisés pour définir les catégories présentées ci-dessus.

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Introduction

Parkinson's disease (PD) is an age-related disorder. However, a subset of people develops PD early in their life. This subset carries significant interest due to its clinical course and increased genetic penetrance. The first large series of subjects with PD starting before the age of 40 was published in 1981 by Japanese authors under the title juvenile parkinsonism (JP).[1,2] Six years later, Quinn et al. published a further 60 such cases from the United Kingdom (UK).[3] It seemed inappropriate to label adult cases as juvenile, so these authors proposed < 40 years for young-onset Parkinson's disease (YOPD) and <21 years for what they called JP – later designated as juvenile-onset Parkinson's disease.[3] Over the years, the age cutoff criteria for young-on set PD have been inconsistent. Thus, while all cases with onset <40 years have been classified as young onset, some have stretched the term young onset to apply to all PD starting before 45, 50, or even 55 years of age.[4–9] The age cutoff to define YOPD has thus been arbitrary, without any sound scientific justification.[10,11] This contentious issue is still unresolved. In the current study, we have categorized JP, YOPD, and early onset Parkinson's disease (EOPD) as follows: JP onset is younger than 20 years (i.e. before their 20th birthday); YOPD subjects have onset after their 20th and before their 40th birthday; and EOPD subjects have onset after their 40th and before their 50th birthday.

Materials and Methods

This report is part of a multicenter study titled "*Genetics Of Pan-Indian Young Onset Parkinson's Disease (GOPI-YOPD)*" conducted under the aegis of the Parkinson Research Alliance of India (PRAI) and MedGenome Labs Pvt Ltd. The subjects were recruited from 10 specialty Movement Disorders Centers/ Neurology clinics across India over a 2-year period. Subjects diagnosed to have developed PD with age at onset ≤50 years, as per the modified UK Brain Bank Criteria (excluding the family history criterion), were included in the study.[12] All the subjects were assessed by movement disorders specialists and had undergone investigations to rule out secondary causes (imaging, metabolic screening, Wilson's disease workup, and others) at the clinical decision of the treating teams. All the patients were under regular follow-up at these clinics. Patients with confirmed alternative diagnosis (like genetics of Huntington's disease) or with clinical red flags were excluded. Clinical and demographic data at recruitment were obtained through a predesigned questionnaire to capture current and past events in relation to PD (supplementary data). The data collection was done on real-time basis to a centralized cloud server using the Google platform. Statistical analysis included Student's "t" test, Fisher's Exact test, analysis of variance (ANOVA), and Pearson chi-square test, based upon categorical and non-categorical values. A "p" value of <0.05 was considered significant.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Institutional Ethics Boards of each center, and written informed consent was taken from each subject.

Data Availability

All the data that support the findings of this study are available from the corresponding author upon request.

Results

Demographics

Six-hundred and sixty-eight subjects from across India with PD onset before the age of 50 were recruited for the study. Among them, 68% were male (M:F 455:213) and the mean age at recruitment was 46.8 ± 8.7 years, range 13–71 years. Most of these cases were sporadic (85%), but 15% ($n = 100$) were familial (one or more other affected relative up to second degree). India is a vast country with varied cultures, ethnicity, and practices; our subjects represent from differing ethnic and geographical regions of India (North – 32.3%, East – 21.5%, South – 36.8%, West – 9.4%). Consanguineous parentage was noted in 13% of the sample. Notably, consanguinity was especially common (77%) in Southern India (Table 1). Religious and cultural aspects varied, with Hindus constituting the majority (84.3%) followed by Muslims (12.6%), Christians (1.3%), Sikhs (1.0%), and Jains (0.4%), the remainder being Parsis and tribals. Educational level varied – 60.8% had education above 10th grade (preuniversity – 21.1%, undergraduate – 23.9%, postgraduate or higher – 15.8%). No formal schooling was documented in 10.6% of subjects. The pattern of geographical distribution and features is shown in Table 1.

Clinical Profile

Mean age at onset of symptoms was 38.7 ± 8.1 (range: 11–50) years, and the average duration of motor symptoms was 96.4 ± 72.0 (range: 2–432) months. Most subjects had asymmetric onset (94%, $n = 629$) and 4.2% ($n = 28$) had symmetric onset based on their history. There was not much difference between right-sided (48.6%) and left-sided onset (45.9%).

The initial presenting clinical motor feature was variable: 89.2% presented with bradykinesia, 76.1% stiffness, 75.5% rest tremor, and 54% change in gait. The motor features at assessment included tremor (81.3%), change in facial expression (73.7%), stiffness (72.3%), generalized weakness (58.7%), leg dragging (58.3%), shuffling of gait (53.5%), micrographia (50.8%), abnormal posture (48.1%), postural imbalance (36.8%), freezing of gait (36.2%), dystonia (20.8%), and falls (19.7%). Modified Hoehn and Yahr stages (H&Y stage) at the time of recruitment

Table 1: Demographic profile and geographical distribution of subjects

	North Indian	East Indian	South Indian	West Indian	Total
No. of subjects (%)	215 (33.3)	144 (21.5)	246 (36.7)	63 (9.4)	668
Age at onset (years, range)	39.3 ± 8.3 (11–50)	39.0 ± 7.4 (17–50)	37.8 ± 8.1 (14–50)	39.2 ± 8.5 (15–49)	38.7 ± 8.1 (11–50)
Male:Female	146:69	97:47	173:73	39:24	455:213
Duration of symptoms (months, range)	104.8 ± 77.9 (2–432)	88.9 ± 63.1 (4–300)	97.2 ± 72.6 (2–360)	78.9 ± 61.7 (6–336)	96.4 ± 72.0* (2–432)
Consanguineous parentage (%)	16 (18.2)	05 (5.7)	62 (77.3)	5 (5.7)	88*
Familial Parkinson's disease (%)	33 (26.8)	28 (22.7)	38 (30.9)	24 (19.5)	123
Educational level (>10th grade) (%)	135 (33.1)	83 (20.4)	151 (37.1)	38 (9.3)	407*

were Stage 1 ($n = 83$), Stage 1.5 ($n = 92$), Stage 2 ($n = 229$), Stage 2.5 ($n = 99$), Stage 3 ($n = 122$), Stage 4 ($n = 29$), and Stage 5 ($n = 14$). The clinical assessment was not done at specific times in relation to medication dosages (i.e. could have been conducted in either ON or OFF phase); hence, the Unified Parkinson's Disease Rating Scale (UPDRS) scoring was variable and not consistent across the group. However, the mean UPDRS III (motor section) score was 28.6 ± 18.3 (range: 1–97).

Nonmotor symptoms, based on history, occurring during the course of the disease, were documented at the time of assessment. The frequency of various nonmotor symptoms included fatigue (53.7%), pain (48.7%), depression (45.6%), anxiety (45.4%), constipation (44.1%), difficulty in falling asleep/staying asleep (33.8%), nocturia (32.1%), apathy (30.5%), excessive sweating (25.9%), REM sleep behavior disorder (RBD) (25.6%), memory/cognitive issues (22.4%), panic attacks (19.4%), sexual dysfunction (19%, M:F 110:17), abnormal bodily sensations (17.8%), sialorrhea (16.4%), excess daytime sleepiness (15.2%), reduced smell sensation (14.5%), falling asleep unintentionally during the day (13.5%), hallucination/delusion/illusions (11.7%), restless leg syndrome (10.2%), light headedness/dizziness/blackout (8.7%), seborrhea (8.7%), periodic leg movements in sleep (7.9%), orthostatic hypotension (3.7%), and urinary dysfunction in the form of urgency/increased frequency (3.2%).

Juvenile versus Young versus Early Onset Parkinson's Disease

The whole cohort was grouped into JP cases ($n = 25$, 3.8%, < 20 years at onset), YOPD cases ($n = 333$, 49.8%, <40 years at onset), and EOPD ($n = 310$, 46%, <50 years at onset) (Table 2).

The presenting features varied between YOPD and EOPD. YOPD subjects more often had dystonia ($p < 0.0001$) and gait impairment as initial symptoms ($p = 0.005$). During the course of the disease, gait issues (including freezing of gait, shuffling, falls, and imbalance) predominated ($p < 0.01$) in YOPD compared with EOPD. Among nonmotor features, depression ($p = 0.03$), and sexual dysfunction ($p = 0.003$) were more common in YOPD. RBD ($p = 0.01$) and urinary dysfunction ($p = 0.003$) were more prevalent in the EOPD group. In YOPD, 39.9% had developed dyskinesias after a mean of 5.7 years of disease symptoms as against 25.5% of EOPD who had developed dyskinesia after 4.4 years of symptoms ($p = 0.001$ Table 2).

Twenty-five subjects (3.7%) had JP (Table 2). In comparison to the rest of the cohort, this group had a higher prevalence of consanguinity, suggesting autosomal recessive inheritance. Unsurprisingly, disease duration from their very early onset of motor symptoms at the time of the study was higher among this group. Dystonia, gait problems, apathy, anxiety, panic attacks, and depression were more common in JP, and their latency to developing dyskinesias was significantly longer, 32% developing dyskinesias after a mean 9.6 years of disease symptoms. Sleep disturbances (RBD and excessive daytime somnolence) were less common in JP.

The EOPD group developed dyskinesias after a shorter duration of motor symptoms than the JP and YOPD groups ($p = 0.001$). Earlier age at onset of PD was associated with higher consanguinity ($p < 0.0001$) and family history of PD. The frequency of dyskinesia was higher in YOPD and JP groups, but they also had a longer duration of symptoms as compared to the EOPD group. The JP group more frequently had dystonic dyskinesia ($p = 0.007$) and OFF dystonia ($p = 0.02$) as compared to the YOPD and EOPD groups.

Treatment Pattern

Most subjects had taken a variety of dopaminergic therapies during the course of their disease. Levodopa–carbidopa combination was the most commonly prescribed (83.1%). Levodopa controlled release formulations were used by 26.8% and add-on entacapone by 19.6%. Dopamine agonists – pramipexole (53.9%), ropinirole (25.3%), and piribedil (1.6%) were used alone or in combination with other classes of drug. Among MAO-B inhibitors, rasagiline was more commonly used (29.7%) than selegiline (3.7%). Amantadine (41.4%) and anticholinergics (52.2%) were also frequently used. Beta blockers were used by a small number (2.8%). Among all 668 subjects, 92.1% had a good response to dopaminergic therapy. The remainder were either not on dopaminergic therapy (5.8%) or a clear, unequivocal response was not appreciated (2.1%) due to the short duration of therapy. Other medications included selective serotonin reuptake inhibitors (10.9%), antipsychotics (5.8%), or benzodiazepines (8.8%) to address neuropsychiatric manifestations (Table 2).

EOPD subjects had mostly used multiple medications during the course of their management. EOPD used more frequently dopamine agonists, monoamine oxidase inhibitors amantadine, and anticholinergics than did the YOPD and JP groups (Table 2).

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Table 2: Comparison between different age groups of Parkinson's disease

Age at onset	JP <20 years	YOPD (20–40 years)	EOPD (40–50 years)	p (JP vs. YOPD vs. EOPD)	p (YOPD vs. EOPD)
Demographic features					
No. of subjects	25	333	310		
Male:Female	18:7	212:121	225:85	0.05	
Mean age at onset, years (range)	17 ± 2.4 (11–20)	34.0 ± 5.0 (21–40)	45.4 ± 2.6 (41–50)	-	-
Duration of symptoms, months (range)	152.6 ± 114.6 (6–360)	105.7 ± 77.4 (2–432)	81.8 ± 56.3 (2–276)	<0.0001*	<0.0001
Age at study inclusion years (range)	31.0 ± 10.0 (16–48)	43.0 ± 7.6 (22–71)	52.2 ± 5.2 (41–70)	<0.0001*	
Consanguineous parentage (%)	14 (53.8)	49 (14.7)	25 (8.0)	<0.0001*	
Family history of PD (%)	6 (23.1)	50 (15.1)	44 (14.2)	0.47	
Clinical features at presentation					
Tremors (%)	19 (76)	264 (79.3)	221 (71.3)	0.94	0.005
Rigidity (%)	19 (76)	265 (79.6)	224 (72.3)	0.24	0.05
Bradykinesia (%)	22 (88)	301 (90.4)	273 (88.1)	0.94	0.69
Gait impairment (%)	17 (68)	196 (58.8)	141 (45.4)	0.018	0.005
Dystonia (%)	9 (36)	86 (25.8)	43 (13.9)	<0.0001	<0.0001
Asymmetric onset (%)	20 (80)	314 (94.3)	294 (94.8)	0.003	0.22
Motor features during the course of management					
Tremors (%)	21 (84)	274 (82.3)	248 (80.0)	0.92	0.65
Bradykinesia (%)	25 (100)	333 (100)	310 (100)	-	-
Freezing of gait (%)	10 (40)	142 (42.6)	90 (29.0)	0.004	0.003
Gait shuffling (%)	15 (60)	201 (60.4)	142 (45.8)	0.02	0.003
Falls (%)	10 (40)	84 (25.2)	37 (11.9)	<0.0001	<0.0001
Postural imbalance (%)	14 (56)	139 (41.7)	92 (29.7)	0.009	0.005
Dyskinesia pattern					
Dyskinesia (%)	8 (32)	133 (39.9)	79 (25.5)	0.001	
Peak dose dyskinesia (%)	7 (28)	109 (32.7)	59 (19.0)	0.0001	
Early morning off dystonia (%)	1 (4)	5 (1.5)	4 (1.2)	0.56	
Biphasic dyskinesia (%)	0 (0)	10 (3)	10 (3.2)	0.66	
Dystonia noted in both "ON" and "OFF" state (%)	5 (20)	24 (7.2)	14 (4.5)	0.007	
Dystonia noted in "OFF" state only (%)	5 (20)	48 (14.4)	25 (8.1)	0.02	
Dystonia noted in "ON" state only (%)	0 (0)	7 (2.1)	4 (1.2)	0.58	
Duration of motor symptoms when dyskinesia was acknowledged (years, range)	9.6 ± 5.2 (2–15)	5.7 ± 3.7 (0–18)	4.4 ± 3.7 (0–17)	0.001*	0.01
UPDRS III (Motor section) score (Random documentation)	33.2 ± 24.7 (4–97)	31.7 ± 18.4 (3–88)	25.2 ± 17.1 (1–72)		
Nonmotor features during the course of symptoms					
Apathy (%)	10 (40)	109 (32.7)	85 (27.4)	0.74	0.54
Anxiety (%)	15 (60)	161 (48.3)	127 (40.9)	0.10	0.06
Panic attacks (%)	9 (36)	65 (19.5)	56 (18.1)	0.11	0.26
Depression (%)	14 (56)	168 (50.4)	123 (39.7)	0.04†	0.03
Hallucination/Delusions/Illusions (%)	3 (12)	47 (14.1)	28 (9.0)	0.30‡	0.12
Memory/cognitive issues (%)	4 (16)	77 (23.1)	68 (21.9)	0.90	0.71
Light headedness/dizziness (%)	2 (8)	34 (10.2)	22 (7.1)	0.76	0.38
Orthostatic hypotension (%)	1 (4)	14 (4.2)	10 (3.2)	0.74	0.87
Constipation (%)	8 (32)	148 (44.4)	139 (44.8)	0.57	0.42

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Table 2: *(Continued)*

Age at onset	JP <20 years	YOPD (20–40 years)	EOPD (40–50 years)	p (JP vs. YOPD vs. EOPD)	p (YOPD vs. EOPD)
Urinary dysfunction (urgency/ frequency/nocturia) (%)	8 (32)	91 (27.3)	116 (37.4)	0.005	0.003
Sexual dysfunction (%)	5 (20)	67 (20.1)	55 (17.7)	0.01	0.02
Excessive sweating (%)	11 (44)	93 (27.9)	69 (22.2)	0.07	0.07
Seborrhea (%)	5 (20)	33 (10)	20 (6.45)	0.18	0.23
Sialorrhea (%)	3 (12)	58 (17.4)	48 (15.5)	0.49	0.21
Unintentionally doze off/fall asleep (%)	2 (8)	41 (12.3)	47 (15.2)	0.59	0.75
Rapid eye movement (REM) sleep behavior disorder (RBD) (%)	5 (20)	72(21.6)	94 (30.3)	0.03†	0.01
Restless leg symptoms (%)	2 (8)	29(8.7)	37 (11.9)	0.49	0.21
Periodic leg movements (%)	2 (8)	22(6.6)	29(9.3)	0.35	0.08
Excessive daytime sleepiness (%)	4 (16)	53(15.9)	44 (14.2)	0.07	0.38
Hyposmia	2 (8)	40(12.0)	55 (17.7)	0.26	0.11
Pain (%)	9 (36)	178(53.4)	139 (44.8)	0.06†	0.04
Fatigue (%)	11 (44)	178(53.4)	170 (54.8)	0.02†	0.01
Medication pattern and frequencies					
Levodopa + carbidopa (%)	21 (84)	265 (79.6)	269 (86.8)	0.05	
Controlled release levodopa + carbidopa (%)	05 (20)	81 (24.3)	93 (30)	0.18	
Entacapone (%)	04 (16)	34 (10.2)	93 (30)	<0.0001	
Pramipexole (%)	08 (32)	130 (39)	223 (71.9)	<0.0001	
Ropinirole (%)	05 (20)	44 (13.2)	120 (38.7)	<0.0001	
Piribedil (%)	02 (8)	00	09 (2.9)	0.001	
Rasagiline (%)	04 (16)	70 (21)	125 (40.3)	<0.0001	
Selegine (%)	01 (4)	03 (0.9)	21 (6.8)	<0.0001	
Amantadine (%)	11 (44)	96 (28.8)	170 (54.8)	0.001	
Anticholinergics (%)	11 (44)	140 (42)	198 (63.9)	<0.0001	

EOPD=early onset Parkinson's disease; UPDRS III=Unified Parkinson's Disease Rating Scale Section III (motor part); YOPD=young-onset Parkinson's disease.
Pearson chi-square test.
$p < 0.05$ = Significant.
*ANOVA.
†Fisher's exact test.

Side Effects

Among the total cohort, 32.9%(M:F 139:81) had developed dyskinesias due to dopaminergic therapy at the time of assessment. The mean age at onset of symptoms in these 220 subjects was 37.1 ± 8.1 years, and the average duration of symptoms when their dyskinesias were first appreciated was 5.4 ± 3.8 years (range: 1 month–18 years). There was no specific sex bias for the development of dyskinesia. Other medication-induced prominent adverse events were reported by 10.3% of subjects. These included psychosis, impulse control disorder, dopamine dysregulation syndrome, and depression.

Imaging

Imaging details were limited in the cohort. Computed tomography (CT) brain was done in 232 subjects and all were noted to have normal findings except in 4 where in nonspecific ischemic changes were documented. Magnetic resonance imaging (MRI) brain was done in 571 patients, among which 1 each had incidental neurofibromatosis and right frontoparietal meningioma; nonspecific ischemic changes/lacuanes/small T2-weighted hyperintensities were noted in 8 patients, and age disproportionate atrophy was documented in 21 patients. Functional imaging (Fluorodopa/Trodat imaging) was done in 31 patients and was reported as consistent with PD in 28 subjects, and in the remaining 3, it was reported as normal.

Discussion

Young-onset and juvenile PD subjects contribute a small percentage (5%–10%) of the overall PD spectrum. The prevalence of YOPD subjects varies in the published literature. They have been reported to account for 5%–7% of all PD in the Western hemisphere and up to 14% in a Japanese study.[13] However, this is probably an overestimate because of referral bias to specialist clinics. The incidence of parkinsonism in the USA is

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about 0.8/100,000/year between 0 and 29 years, increasing to 3/100,000/year between 30 and 49 years of age.[13,14] These young-onset subjects differ from older onset subjects in terms of their clinical variability, membership of a productive age group, and variable responses to therapy. There have been a number of studies in the past 30 years reporting the clinical features of EOPD from different parts of the globe.[3–9,12,14–24] The current study has examined a large number of JP, YOPD, and EOPD subjects in the Indian subcontinent (Table 3).

The clinical picture of YOPD has been reported as significantly different from the generality of PD subjects. One group[3] noted that their YOPD subjects, all of whom had akinesia and rigidity, had less frequently developed rest tremor (46%). Subsequently another study,[25] comparing young (≤45 years) versus late (>45 years) onset PD, found that the former more often had rigidity, along with more frequent "off" dystonia. In contrast, 75.5% of our subjects had tremor and 76.1% stiffness as their initial manifestation. The first major publication from India included 30 subjects with JP and YOPD (≤40 years), almost all of whom presented with tremor.[16] Hence, it does appear that the clinical presentation of Indian YOPD subjects is different as compared to the Western experience. Similarly, in a series of 60 subjects with EOPD (≤49 years) from the USA, tremor was the predominant presenting symptom (58.3%).[24] Hence the notion that early onset PD is mostly akinetic-rigid may not be accurate.

YOPD also tends to be different in relation to levodopa therapy and response outcomes. Thus, a UK group found that dyskinesias and motor fluctuations were more frequent and earlier in this age group.[3] However, there was no correlation between the duration of disease before instituting levodopa and delay in subsequent development of motor complications. They also found that early morning "off" dystonia and early morning sleep benefit were more common (each 59%) in this subset. Subsequently, an extended series of 149 YOPD and JPD subjects was published in 1998. Remarkably, more than 25% had developed complications of levodopa therapy within a week of initiation, almost 40% within 6 months, and 91% by 5 years of treatment.[26] In another series comparing early, middle, and late-onset PD, the frequency of dyskinesia and dystonia was lower with increasing age of onset.[24] An Indian group found that about 50% of subjects developed dyskinesia in their YOPD group and 33% in their juvenile PD group at the end of 6 months of therapy.[16] Another study from India in 2005 noted that about 40% of EOPD (≤50 years) had dyskinesias after 5 years of levodopa therapy.[27] In the current series, about 33% had developed dyskinesias due to dopaminergic therapy at the time of assessment. Their average duration of symptoms when dyskinesias were first appreciated was 5.4 ± 3.8 years (range: 1 month–18 years). This pattern is close to that in regular PD subjects (>50 years).

The commonest nonmotor symptoms in our YOPD group were depression (45.6%), anxiety (45.4%), and apathy (30.5%). A similar rate of depression (48.3%) was also noted in a USA group.[24] The current study has not explicitly looked at long-term survival and outcomes in YOPD in comparison to regular PD cases. A comparative study in 2014, involving EOPD (≤49 years), middle-onset (50–69 years), and late-onset (≥70 years) subjects, noted that among these groups the EOPD cases had a more frequent positive family history, longer survival, non-tremor presentation, and depressive symptoms.[24]

As mentioned in the introduction, the age cutoff used for YOPD has been arbitrary and has varied over the years.[10,11] The 1987 UK study used < 40 years to define YOPD.[3] However, since then a number of studies including cases with onset up to 45 or 50 have been labeled young onset.[4–6,8,9,20–22,24] Thus, the terminology YOPD and EOPD has been interchangeably used, without clear demarcation. In our series, we have examined the differences between YOPD (<40 years) versus EOPD (<50 years) subjects. The younger age group have more consanguineous parentage, indicating higher genetic penetrance and autosomal recessive inheritance. In addition, the younger age group (<40 years) had more frequent dystonia ($p < 0.0001$) and gait impairment ($p = 0.01$) at presentation. During the course of the disease, YOPD subjects have more gait and balance-related issues than EOPD subjects. Our YOPD subjects also had differences in nonmotor symptoms, with depression and sexual dysfunction being more common, and REM sleep behavior disorders being less frequent, than those with EOPD. Dyskinesia frequency was higher in the YOPD group (39.9% vs. 25.5%), and their duration of symptoms at the point of dyskinesia development was longer in the YOPD than in the EOPD group. The specific relation between symptom duration, duration of treatment, and cumulative dosage of levodopa at the point of development of dyskinesias was not recorded in the study. This delayed development of dyskinesias is at variance with other studies, which have found that YOPD subjects develop dyskinesia very early in their disease course.[16,26] This difference could be related to introducing more cautious therapeutic paradigms in YOPD or other factors, including genetic.

The overall picture indicates that YOPD subjects are clinically different from those with EOPD. Whether this EOPD group is the same as other regular PD subjects (50+ years), or forms a separate subgroup, is not addressed in our cohort. In this era of precision medicine, proper clinical and genetic categorization of the patients would be very critical for appropriate workup, and thrust to conduct interventional trials either for neuroprotection/disease modification.

Our large study inevitably has some limitations. First, it is cross-sectional rather than longitudinal/perspective, so some of the historical data points could be inaccurate when recollected by the subjects/caregivers. However, these subjects were on regular follow-up at these centers, which followed them clinically. Second, the genetic analysis for other genetic causes like neurodegeneration with brain iron accumulation, dystonia genes were not available, which is more so important in the juvenile group. Most of these subjects had a long duration of symptoms at the time of recruitment (e.g. mean of 12 years in JP) with no clinical red flags and good response to dopaminergic therapy to substantiate their inclusion. Patients who had an alternative diagnosis (like Wilson's disease, Huntington's Disease, etc.) either biochemically or genetically were not screened/included in the study. Third, some of the clinical data points (like eye movements) and detailed imaging findings were not collected comprehensively (supplementary data). Fourth, although DNA samples have been donated by all subjects, analysis has not yet been performed. Finally, we do not yet know whether this data can be used to generalize across different ethnic backgrounds and geographical areas across the world.

To conclude, this large series of 668 Indian JP, YOPD, and EOPD subjects gives significant insights into their clinical profile.

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Table 3: Overview of various young/early onset Parkinson's disease studies from across the literature

Study	Country	Age cutoff criteria	Title/terminology used	Time of study, (duration of study, years)	No. of subjects	Age at onset – mean + SD, (range) years	M:F	Duration of symptoms – mean + SD, (range)	Family history of PD – % (n)
Current study, 2020	India	≤50	JP, YOPD,EOPD	2017–19 (2 years)	668	38.7 ± 8.1 (11–50)	455:213	96.4 ± 72.0 (2–432) months	14.9% ($n = 100$) YOPD-12%, JP – 23%
Quinn N,[3] et al., 1987	United Kingdom	≤40	YOPD JPD	1981–86 (6 years)	60	35 (median)	46:24	–	~20% (YOPD) 100% (JP)
Gibb WR,[25] 1988	United Kingdom	≤45	YOPD	–	46	38 (median) (24–45)	–	11 (1–34), years	–
Giovannini P,[17] 1991	Italy	≤40	EOPD	–	60	34.7 (24–39)	38:22	10.4 (0.6–30), years	–
Muthane U,[16] 1994	India	≤41	JPD and YOPD (Both combined as EOPD)	–	30	32.4 (YOPD) 17.9 (JP)	20:10	–	12% (YOPD) 14% (JP)
Gomez AG,[15] 1997	Argentina	≤40	EOPD	–	34	35 ± 5 (21–40)	23:11	9.6 ± 6 (1.5–23), years	–
Schrag A,[26] 1998	United Kingdom	≤40	YOPD	17 years	149	34 (YOPD) 17 (JP) (5–39 yrs)	96:53	18 (YOPD) 24 (JP) 2–45 years	18.1%
Klein C,[4] 2005	Italy	≤50	EOPD	–	65	43.2 ± 5.4 (45–51)	31:34	–	5% ($n = 3$)
Clark LN,[5] 2006	USA	≤50	EOPD	–	101	41.1 ± 7.2	–	11.7 ± 8.0, years	13% ($n = 13$)
Choi JM,[6] 2008	Korea	≤50	EOPD	–	72	38.8 ± 7.0 (13–50)	34:38	–	16.7% ($n = 12$
Lee MJ,[7] 2008	Taiwan	≤50	EOPD	–	68	40.1 ± 7.0 (18–49)	26:42	9.5 ± 6.0 (1–26), years	14.7 % ($n = 10$)
Mellick GD,[8] 2009	Australia	≤50	EOPD	2000–05 (5 years)	74	42.4 ± 5.7	44:30	~16 years	40.5% ($n = 30$)
Macedo MG,[9] 2009	Netherlands	≤50	EOPD	2003–07 (5 years)	187	41.1 ± 6.6 (16–50)	122:65	11.4 ± 6.8 years	27% ($n = 50$)
Camargos ST,[18] 2010	Brazil	≤40	EOPD	2006 (1 year)	45	34.8 ± 5.4	–	–	17.8% ($n = 8$)
Guo J,[21] 2010	China	≤50	EOPD	2000–08 (8 years)	127	40 ± 8.4 (19–50)	86:41	4.3 ± 3.2, years	–
Kilarski LL,[23] 2012	United Kingdom	≤45	EOPD	–	136	37 (median)	76:60	–	11.5%
Monroy-Jaramillo,[19] 2014	Mexico	≤45	EOPD	–	127	34.9 ± 8.1 (13–45)	73:54	–	31.1% ($n = 38$)
Mehanna R,[24] 2014	USA	≤49	YOPD	2002–10 (8 years)	60	–	57:03	–	20% ($n = 12$)
Erer S,[22] 2016	Turkey	≤50	EOPD	2013–14 (2 years)	50	39.2 ± 8.4	26:24	–	36% ($n = 18$)
Youn J,[20] 2019	Korea	≤50	EOPD	7 months	70	44.7 ± 0.6	33:37	–	5.7%
Tan MMX,[28] 2019	United Kingdom	≤50	YOPD	–	424	~42 years	–	–	~25.7%

EOPD=early onset Parkinson's disease; JP=juvenile parkinsonism; JPD=juvenile Parkinson's disease; YOPD=young-onset Parkinson's disease.

With this current sample size, various notional impressions of YOPD, such as initial rigid presentation and very early onset dyskinesias, are subject to question. All subjects have donated DNA samples, analysis of which will undoubtedly throw new light on these issues. When our DNA results become available, it will be interesting to compare our findings with recent genetic data from the UK,[28] China,[29] and France.[30]

Supplementary Material

To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2021.40.

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Conflicts of Interest

There are no conflicts of interest.

Statement of Authorship

PLK: Design and conceptualized study; analyzed the data; interpreted the data; drafted the manuscript for intellectual content; VG: Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content; TSG: Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content; RMK: Design and conceptualized study; analyzed the data; interpreted the data; drafted the manuscript for intellectual content; HK: Design and conceptualized study; analyzed the data; interpreted the data; drafted the manuscript for intellectual content; RB: Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content; AM: Interpreted the data; revised the manuscript for intellectual content; PMW: Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content; RY: Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content; SD: Interpreted the data; revised the manuscript for intellectual content; NK: Interpreted the data; revised the manuscript for intellectual content; RG: Interpreted the data; revised the manuscript for intellectual content; AB: Interpreted the data; revised the manuscript for intellectual content; PKP: Interpreted the data; revised the manuscript for intellectual content; UBM: Conceptualization and Data acquisition; DSK: Conceptualization and Data acquisition; NQ: Major interpretation of the data, analysis and revision of manuscript for intellectual content; RVL: Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content.

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