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Long-duration Parkinson's disease: Role of lateralization of motor features

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Abstract

Background—A mean of 10 years elapse before patients with Parkinson's disease (PD) reach Hoehn & Yahr (H&Y) stage 4, and 14 years for stage 5. A small proportion of PD patients survive and are ambulatory for ≥20 years. We sought to identify features associated with long-duration PD (dPD).

Methods—This five-center, case–control study compared 136 PD patients with ≥20 years of duration and H&Y stage ≤4 (dPD) to 134 H&Y-, age- and gender-matched PD patients between 10 and 15 years of disease (cPD).

Results—By study design, there were no between-group differences in age, gender and H&Y. dPD subjects were younger at onset ($p < 0.0001$), had more psychosis (p: 0.038), were receiving higher levodopa equivalent daily doses (p: 0.02), were predominantly left-handed (p: 0.048), and had greater frequency of left-sided onset (p: 0.015) compared to cPD subjects. Both groups had similar rates of resting tremor, dementia and REM sleep behavior disorder.

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Conclusions—Early disease onset, left-handedness and left-sided onset are associated with long disease and ambulatory PD survival. The neurobiological basis of the prognostic value of lateralization deserves further investigation.

Keywords

Parkinson's disease; Longevity; Handedness

1. Introduction

Several studies have highlighted the phenotypic heterogeneity of Parkinson's disease (PD) [1,2], and attempted to delineate subtypes according to rate of disease progression, prevalence of tremor, and age of onset. Although previous reports have suggested that the tremor-dominant variant of PD might be associated with slower rate of progression and lower functional disability [3,4], more recent studies have not confirmed this association [5]. On the other hand, greater baseline impairment, older age [5,6] and the presence of specific non-motor features such as cognitive impairment, psychosis and REM sleep behavior disorder (RBD) [5,7] may predict more severe disease and rapid accrual of disability.

Several measures have been used to assess disability and disease progression in PD, such as the Hoehn and Yahr (H&Y) scale [8], the Unified Parkinson's disease Rating Scale (UPDRS), and time to milestones such as falls, hallucinations, dementia, and institutionalization [9]. In Hoehn and Yahr's seminal study conducted in the pre-levodopa era, [8], H&Y stages 4 and 5 were reached 9 and 14 years after diagnosis, respectively. Survival, as measured by the time from onset of motor symptoms to death, provides an indirect estimate of disease severity and rate of progression [5]. Median survival from motor onset was 15.8 years in a recent prospective community-based study of 230 PD patients, whereby approximately 70% of patients died before 20 years [10]. Survival for or beyond 20 years is uncommon, representing a small percentage of the clinic population, even at specialized centers, This population may be even smaller when considering those who survive and remain ambulatory, representing the top 5% of PD survivors [10].

The aim of the present study was to identify clinical features associated with long-duration PD, defined as those with a disease course ≥20 years and still able to walk or stand unassisted (H&Y ≤ 4).

2. Methods

2.1. Subjects and design

We designed a five-center, case–control study comparing PD patients with disease duration of at least 20 years (dPD) with a control group of PD patients with 10–15 years (cPD) matched for age, gender, and to H&Y stage ≤ 4. Patients were selected consecutively from five tertiary movement disorders clinics, on the basis of these pre-defined criteria. Diagnosis of PD was established by movement disorders experts using the Queen Square Brain Bank criteria [11]. This study was approved by each of the local ethics committees of the participating centers and patients provided informed consent for collection of demographic and clinical data.

2.2. Measurements

Standardized data collection included demographics, handedness, side of onset, disease duration, levodopa equivalent daily dose (LEDD) and the presence of non-motor symptoms (psychosis, dementia and RBD) at the time of data collection. Disease duration was defined

by the approximate time from symptom onset to the time of data collection. Handedness was defined using the Edinburgh inventory [12]. Data on handedness were also collected from 249 spouses of patients who attended the participating centers, to define the distribution of hand dexterity in non-PD subjects of similar age. Motor subtypes were classified as tremor and non-tremor-dominant according to the presence of rest tremor at the time of PD diagnosis. Motor asymmetry was defined as the most affected side at the time of the most recent examination of the cardinal signs of parkinsonism. Dementia was classified according to DSM-IV criteria [13]. Psychosis was defined according to the NINDS/NIMH diagnostic criteria for psychosis [14]. These criteria include the presence of at least one of the following: illusions, false sense of presence, hallucinations or delusions, which are recurrent or continuous for at least one month, detected at any time since disease onset. Clinically probable RBD (cpRBD) was ascertained by the criteria proposed by the American Sleep Disorders Association [15]. This clinical classification has been used and validated in recent studies on this parasomnia [16]. LEDD was calculated based on the formula published by Tomlinson et al. [17].

2.3. Statistical analyses

Data were compared using *t*-test for means and the *chi*-square test with Yates correction for continuity or Fisher exact tests for categorical and ordinal data. Differences were considered significant for p values <0.05.

3. Results

3.1. Patient characteristics

A total of 136 patients were included in the dPD and 134 in the cPD groups (Table 1). The total of dPD patients represented approximately 5% of patients with PD seen at the participating centers. As anticipated by design, there were no between-group differences in age, gender, or H&Y.

3.2. Effect of disease duration

Besides longer disease duration by study design (23.2 ± 4.5 vs. 10.7 ± 1.2 years), dPD subjects had larger mean LEDD (1004.4 ± 457.2 vs. 840.5 ± 283.4 mg, p: 0.02), younger age at onset (47.1 ± 10.5 vs. 59.2 ± 12.5 years; $p < 0.0001$) and greater prevalence of psychosis (55.9% vs. 43.3%; p: 0.038, Yates correction: 0.05) compared to cPD.

3.3. Effect of disease lateralization

Although subjects with left-sided handedness were a minority in both groups, they were overrepresented in the dPD group (9.5% vs. 3%; p: 0.026, Yates correction: 0.048). Among 248 control subjects screened for handedness, only 10 (4%) were left-handed. Subjects in the dPD group had more frequent left-sided onset (62.5% vs. 47.7%; p: 0.015, Yates correction: 0.02) than in the cPD group. To explore the possibility that some patients may have been forced to change their hand preference during the disease course due to limitations imposed by the disease, we compared the frequency of right handed individuals between those with right and left side onset, showing similar frequencies (92.1% vs. 91.8%; p: 0.99). Similarly, among left-handed patients, 61.5% had left side onset and among right handed cases, 63% had left side onset (p: 0.86).

Both groups had similar rates of resting tremor (78.7% vs. 83.6%), dementia (31.6% vs. 28.8%; p: 0.75) and cpRBD (59.6% vs. 58.2%; p: 0.82).

4. Discussion

We found that still-ambulatory patients living with PD for at least 20 years had earlier disease onset, were more frequently left-handed, had motor signs lateralized predominantly to the left hemibody, and also exhibited psychosis more frequently than subjects with similar disability but less than half their disease duration. Interestingly, we found no between-group differences in tremor phenotype and selected non-motor features (dementia and cpRBD), as previously reported [8,10,18].

It is certainly surprising that the rate of dementia was similar between two groups with widely different preselected disease durations. Since the risk of dementia is primarily influenced by disease duration and the prevalence of resting tremor tends to decline over time even among those considered tremor-dominant [19], it is therefore plausible that the dPD group would have had a lower prevalence of dementia and a higher prevalence of resting tremor than the cPD group if the cohorts could have been compared at a similar time point from symptom onset, an impossibility given the design of this case–control study.

On the other hand, increased frequency of hallucinations in the dPD group may be expected by the significantly higher mean LEDD and longer disease duration, which are, along with disease severity, strong predictors of PD-related psychosis [20]. Alternatively, the presence of psychosis may reflect a burden of regional Lewy-body pathology distribution that may differ according to disease duration [21]. Whereas hallucinations in PD are correlated with Lewy-body deposition in limbic regions [22], cognitive dysfunction is also influenced by age-related changes (vascular, tau/beta amyloid load, white matter pathology) [19]. RBD is also closely linked to disease severity, although duration, age and lower tremor scores have been previously implicated [7].

Although the study groups were matched for disease severity (H&Y stage), the dPD group received significantly greater LEDD to achieve a clinical functionality similar to that of the cPD group. This may be explained by the higher therapeutic threshold as the disease progresses, compounded by a progressively briefer and weaker short-duration response for levodopa [23].

The novel findings of our study are that dPD patients are more likely to be left-handed and to have greater motor burden on the left hemibody. A previous post-hoc study on the DATATOP cohort showed that those affected in the left side needed levodopa earlier, the pre-defined study endpoint [24]. It is plausible to argue that earlier initiation of dopaminergic therapy among those with left-sided predominant PD patient may have had a favorable disease-modifying effect compared to those with right-sided onset who had ‘delayed’ onset of therapy. Although this is an intriguing hypothesis, our study was not designed or powered to examine the effect of timing of treatment initiation on survival or disease progression.

Left-handedness has been associated with superior spatial ability, numerical reasoning, verbal reasoning, hand skills, higher incidence of migraine, essential tremor, and schizophrenia [25,26]. Handedness in PD appears to be related to the side of asymmetric disease, with left-handed individuals tending to have more severe disease on the left side of the body [27,28]. Few studies have analyzed non-motor symptoms in regards to laterality of parkinsonism but the available data suggests that right-sided-predominant PD patients may behave worse than left-sided-predominant PD [29]. PD patients with right-sided-predominant motor deficits were reported to be more impaired on neuropsychological tests of dominant hemisphere function and were more likely to develop worse cognitive scores, as measured by the MMSE [30].

Our study has several limitations, including retrospective data collection, clinical but not polysomnographic RBD identification, dementia ascertained by screening instruments rather than neuropsychological evaluations, and group matching using the H&Y scale, which is weighted on motor rather than non-motor symptoms. The issue of non-motor symptoms is particularly important for its impact on patients' quality of life, specially at more advanced disease stages, although they have been documented at the earliest phases of PD when screened with more specific and sensitive evaluation tools [31,32]. Additionally, although the difference in the proportion of left-handedness between groups was statistically significant, the absolute number of left-handed patients is relatively small. Finally, the definition of dPD was arbitrary. The criteria used were intended to reflect two solid metrics of a clearly favorable disease course: long survival and preserved ambulation. Considering how infrequent it is to find ambulatory patients with more than 20 years of disease duration, it is reasonable to assume that, in these individuals, the degree and rate of progression of disability is less aggressive than that of most PD cases. According to prior studies, the dPD cohort represents the top 5% of survival [10]. On the other hand, this may be thought of as a reflection of better general health or earlier disease onset, although the mean age at onset of our sample of dPD patients did not meet criterion for "early onset" PD (under 40 years of age). Nevertheless, by studying this group of "long survivors", we have identified intriguing differences in sidedness and asymmetry that deserve further examination as potential markers of comparatively longer disease duration and overall more "benign" still-ambulatory PD.

References

[1]. van Rooden SM, Heiser WJ, Kok JN, Verbaan D, van Hilten JJ, Marinus J. The identification of Parkinson's disease subtypes using cluster analysis: a systematic review. Mov Disord. 2010; 25:969–78. [PubMed: 20535823]

[2]. Lewis SJ, Foltynie T, Blackwell AD, Robbins TW, Owen AM, Barker RA. Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach. J Neurol Neurosurg Psychiatry. 2005; 76:343–8. [PubMed: 15716523]

[3]. Poewe WH, Wenning GK. The natural history of Parkinson's disease. Neurology. 1996; 47:S146–52. [PubMed: 8959983]

[4]. Jankovic J, Kapadia AS. Functional decline in Parkinson disease. Arch Neurol. 2001; 58:1611–5. [PubMed: 11594919]

[5]. Marras C, Rochon P, Lang AE. Predicting motor decline and disability in Parkinson disease: a systematic review. Arch Neurol. 2002; 59:1724–8. [PubMed: 12433259]

[6]. Kempster PA, O'Sullivan SS, Holton JL, Revesz T, Lees AJ. Relationships between age and late progression of Parkinson's disease: a clinico-pathological study. Brain. 2010; 133:1755–62. [PubMed: 20371510]

[7]. Lee JE, Kim KS, Shin HW, Sohn YH. Factors related to clinically probable REM sleep behavior disorder in Parkinson disease. Parkinsonism Relat Disord. 2010; 16:105–8. [PubMed: 19716333]

[8]. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology. 1967; 17:427–42. [PubMed: 6067254]

[9]. Kempster PA, Williams DR, Selikhova M, Holton J, Revesz T, Lees AJ. Patterns of levodopa response in Parkinson's disease: a clinico-pathological study. Brain. 2007; 130:2123–8. [PubMed: 17586867]

[10]. Forsaa EB, Larsen JP, Wentzel-Larsen T, Alves G. What predicts mortality in Parkinson disease?: a prospective population-based long-term study. Neurology. 2010; 75:1270–6. [PubMed: 20921512]

[11]. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry. 1992; 55:181e4. [PubMed: 1564476]

[12]. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. 1971; 9:97e113. [PubMed: 5146491]

[13]. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed.. DSM IV; Washington, DC: 1994.

[14]. Ravina B, Marder K, Fernandez HH, Friedman JH, McDonald W, Murphy D, et al. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. Mov Disord. 2007; 22:1061–8. [PubMed: 17266092]

[15]. American Academy of Sleep Medicine. ICSD e International classification of sleep disorders, revised: diagnostic and coding manual. Chicago, IL: 2001.

[16]. Gjerstad MD, Boeve B, Wentzel-Larsen T, Aarsland D, Larsen JP. Occurrence and clinical correlates of REM sleep behaviour disorder in patients with Parkinson's disease over time. J Neurol Neurosurg Psychiatry. 2008; 79:387–91. [PubMed: 17557796]

[17]. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord. 2010; 25(15):2649–53. [PubMed: 21069833]

[18]. Louis ED, Tang MX, Cote L, Alfaro B, Mejia H, Marder K. Progression of parkinsonian signs in Parkinson disease. Arch Neurol. 1999; 56:334–7. [PubMed: 10190824]

[19]. Rajput AH, Voll A, Rajput ML, Robinson CA, Rajput A. Course in Parkinson disease subtypes: a 39-year clinicopathologic study. Neurology. 2009; 73:206–12. [PubMed: 19620608]

[20]. Williams DR, Lees AJ. Visual hallucinations in the diagnosis of idiopathic Parkinson's disease: a retrospective autopsy study. Lancet Neurol. 2005; 4:605–10. [PubMed: 16168928]

[21]. Aarsland D, Larsen JP, Cummins JL, Laake K. Prevalence and clinical correlates of psychotic symptoms in Parkinson disease: a community-based study. Arch Neurol. 1999; 56:595–601. [PubMed: 10328255]

[22]. Harding AJ, Stimson E, Henderson JM, Halliday GM. Clinical correlates of selective pathology in the amygdala of patients with Parkinson's disease. Brain. 2002; 125:2431–45. [PubMed: 12390970]

[23]. Nutt JG, Holford NH. The response to levodopa in Parkinson's disease: imposing pharmacological law and order. Ann Neurol. 1996; 39:561–73. [PubMed: 8619540]

[24]. McDermott MP, Jankovic J, Carter J, Fahn S, Gauthier S, Goetz CG, et al. The Parkinson Study Group. Factors predictive of the need for levodopa therapy in early, untreated Parkinson's disease. Arch Neurol. 1995; 52:565–70. [PubMed: 7763203]

[25]. Biary N, Koller W. Handedness and essential tremor. Arch Neurol. 1985; 42:1082–3. [PubMed: 4051838]

[26]. Dragovic M, Hammond G. Handedness in schizophrenia: a quantitative review of evidence. Acta Psychiatr Scand. 2005; 111:410–9. [PubMed: 15877707]

[27]. Uitti RJ, Baba Y, Whaley NR, Wszolek ZK, Putzke JD. Parkinson disease: handedness predicts asymmetry. Neurology. 2005; 64:1925–30. [PubMed: 15955945]

[28]. Yust-Katz S, Tesler D, Treves TA, Melamed E, Djaldetti R. Handedness as a predictor of side of onset of Parkinson's disease. Parkinsonism Relat Disord. 2008; 14:633–5. [PubMed: 18346926]

[29]. Cubo E, Martin PM, Martin-Gonzalez JA, Rodríguez-Blázquez C, Kulisevsky J, ELEP Group Members. Motor laterality asymmetry and nonmotor symptoms in Parkinson's disease. Mov Disord. 2010; 25:70–5. [PubMed: 20014110]

[30]. Cooper CA, Mikos AE, Wood MF, Kirsch-Darrow L, Jacobson CE, Okun MS, et al. Does laterality of motor impairment tell us something about cognition in Parkinson disease? Parkinsonism Relat Disord. 2009; 15:315–7. [PubMed: 18793864]

[31]. Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, et al. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord. 2009; 24:1641–9. [PubMed: 19514014]

[32]. Chaudhuri KR, Martinez-Martin P, Schapira AH, Stocchi F, Sethi K, Odin P, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. Mov Disord. 2006; 21:916–23. [PubMed: 16547944]

Table 1

Clinical and demographic features of PD patients.

	dPD (*n* = 136)	cPD (*n* = 134)	*P*	OR	CI 95%
Sex (M)	71 (52.2%)	72 (53.7%)	0.99	1	0.62–1.61
Age±SD (range, median)	70.4±10 (44–92, 71)	68.9±12.3 (35–94, 71)	0.26		
Age at onset±SD (range, median)	50.1±7.9 (22–70, 49)	58.2±13.4 (23–87,61)	<0.0001		
PD Duration±SD (range, median)	23.2±4.5 (20–49, 22)	10.7±1.2 (10–14, 10)	<0.0001		
Handedness (L)	13 (9.5%)	4(3%)	0.026	6.34	1.4–29.11
Asymmetry (L)	85 (62.5%)	64 (47.7%)	0.015	1.82	1.12–2.96
H&Y	3.41 (0.6)	3.36 (0.63)	0.47		
Hallucinations	76 (55.9%)	58 (43.3%)	0.038	1.66	1.03–2.68
Dementia	43 (31.6%)	40 (28.8%)	0.75	1.09	0.65–1.82
cpRBD	81 (59.6%)	78 (58.2%)	0.82	1.06	0.65–1.72
TPD	107 (78.7%)	112 (83.6%)	0.3	0.72	0.39–1.34
Mean LEDD±SD (mg)	1004.4±457.2	840.5±283.4	0.02		

M = male; L = left; PD = Parkinson's disease; H&Y = Hoehn and Yahr stage; cpRBD = clinically probable REM sleep behavior disorder; TPD = tremor dominant Parkinson's disease; LEDD = levodopa equivalent daily dose; dPD = Long-duration Parkinson's disease (disease duration > 20 years, H&Y ≤ 4); cPD = Control Parkinson's disease (disease duration = 10–15 years, H&Y ≤ 4). OR = odds ratio. CI = confidence interval. The data are shown as mean±standard deviation (range, median).