How much time is needed in clinical practice to reach a diagnosis of clinically established Parkinson's disease?

Malco Rossi, MD, PhD[a,b]; Santiago Perez Lloret, MD, PhD[b-e]; Marcelo Merello, MD, PhD[a-c].

[a] Movement Disorders Section, Neuroscience Department, Fleni, Buenos Aires, Argentina

[b] National Research Council (CONICET), Buenos Aires, Argentina

[c] Faculty of Medicine, Pontifical Catholic University of Argentina, Buenos Aires, Argentina

[d] Universidad Abierta Interamericana, Centro de Altos Estudios en Ciencias Humanas y de la Salud (UAI-CAECIHS), Buenos Aires, Argentina

[e] Department of Physiology, Faculty of Medicine, University of Buenos Aires, Argentina

Corresponding author

Malco Rossi, MD, PhD

Movement Disorders Section, Neuroscience Department, Fleni.

Montañeses 2325 - Ciudad Autónoma de Buenos Aires (1428) – Argentina. Telephone: +54-011-57773200; E-mail: mrossi@fleni.org.ar

Keywords: Parkinson's disease, parkinsonism, diagnosis, criteria, accuracy

Funding sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest: The authors do not have any competing interest.

Ethical statement: This study was approved by the local Institutional Review Board and informed consent was obtained. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Authors' contributions: All authors made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

ABSTRACT

Introduction: The implementation of accepted clinical diagnostic criteria has improved the accuracy of a clinical diagnosis of Parkinson's disease (PD). Time frames of 3 to 10 years have been empirically proposed to reach a diagnosis of clinically established PD.

Methods: We explored the time to a Final Clinical Diagnosis (FCD) and the factors that predict faster diagnoses in patients presenting with parkinsonism and/or tremor between 2009 and 2015 at our tertiary center. All patients underwent a standardized workout process to reach a FCD, which included an acute levodopa challenge (LDC) after the first visit.

Results: Among the 326 patients included, 215 (66%) received a FCD within the first six months after the LDC. A FCD was reached in 95% and 100% of patients in 33 and 108 months, respectively. PD was the FCD in 196 patients (60.1%). The FCD was reached faster in patients with a positive response to levodopa and when the FCD was PD.

Conclusion: The time needed to reach a final diagnosis in the clinical setting was 2.75 years in 95% of patients presenting initially with parkinsonism and/or tremor. Patients with positive responses to levodopa at the LDC, benefited from shorter delays until the FCD.

Introduction

Differential diagnoses of Parkinson's disease (PD) include neurodegenerative atypical parkinsonism, such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal syndrome (CBS) and dementia with Lewy bodies (DLB), as well as other non-degenerative conditions, such as essential tremor, drug-induced parkinsonism, vascular parkinsonism and normal pressure hydrocephalus [1]. Although the definitive diagnosis can only be reached by a brain autopsy, a clinical diagnosis can be obtained by applying predefined diagnostic criteria, such as the UK Parkinson's Disease Society Brain Bank (UKPDSBB) criteria [2], and the most recently developed International Parkinson and Movement Disorders Society (MDS) Clinical Diagnostic Criteria for PD [3]. Recent data suggest that the latter has an overall accuracy for probable PD of 92.6% [4]. For patients with a disease duration fewer than 5 years, the specificity of a clinically probable PD diagnosis was 87% [4]. Both UKPDSBB and MDS Clinical Diagnostic Criteria for PD criteria propose time frames of 3, 5, or even 10 years during which the detection of some of the clinical aspects of the disease would allow to reach unequivocal diagnoses of clinically established PD. Such time frames have been established based on empirical and unsystematic evidence. For research purposes, the concept of clinically established "Early PD" has been recently proposed based on a modified version of the MDS criteria by removing all disease duration components and changing red flags to absolute exclusions, showing a 95.4% specificity [5]. A clinicopathological study showed an accuracy of the clinical diagnosis of PD as modest as 53% in those patients with less than 5 years of disease duration and response to dopamine replacement therapy, which increased to 88% after more than 5 years of disease duration [6]. Furthermore, the accuracy was only 26% for a clinical diagnosis of PD in untreated or not clearly responsive individuals, suggesting that early diagnosis of

less affected cases unresponsive to initial dopamine replacement therapy should be carefully interpreted and reconsidered over time [1,6]. The main objective of this study was to assess the time to a firm final clinical diagnosis (FCD) of patients presenting with parkinsonism and/or tremor, and to identify factors predicting a more rapid diagnosis.

Methods

Study sample and diagnostic procedure

We conducted a review of medical records of patients with parkinsonism and/or tremor seen for the first time between January 2009, through December 2015. As shown in Figure 1, after an initial visit to a movement disorders specialist when the diagnosis of parkinsonism was made, an acute levodopa challenge (LDC) [7,8] was indicated. The LDC was conducted by a movement disorders specialist at least 72 hours after pre-treatment with domperidone to prevent levodopa–carbidopa-related adverse events. At the time of the LDC patients were not receiving dopaminergic agents. Patients received a single-dose of 250 mg/25 mg levodopa-carbidopa in the fasting state, when motor status was evaluated with MDS-UPDRS-III. Clinical scores were evaluated at baseline, every 15-minute intervals, and at any other time during the evaluation if the examiner, a movement disorders specialist, noted a significant modification in the motor status. Monitoring continued either until the patient returned to baseline status or until 4 hours had elapsed. We considered that improvements of at least 25% in the MDS-UPDRS-III baseline score indicated a "positive" response to levodopa [7,8]. The 25% threshold for the newer MDS-UPDRS-III scale, which is roughly similar to the 30% cut off value used for the older UPDRS motor component [3], was used according to previous studies [7,8]"

Patients were followed by periodic visits, spaced by a mean of three months. The FCDs were based on: a) the LDC result; b) a sustained response to dopamine replacement therapy as subjectively reported by patients and objectively assessed by the treating physician through changes in the MDS-UPDRS-III scale; c) the UKPDSBB and/or MDS Clinical Diagnostic criteria; d) the established diagnostic criteria for atypical parkinsonism (i.e., MSA [9], PSP [10], CBS [11], DLB [12]); e) the presence or absence of 'red flags' for the suspected clinical diagnosis; f) blood and urine routine work-up studies, including copper metabolism; g) olfactory testing (extended version of the Sniffin' Sticks Test - Burghart Messtechnik, Wedel, Germany [8]; h) MRI imaging; and i) DAT-scan (if needed). The FCD was established after clinical certainty existed in at least two consecutive visits. The FCD considered were PD, MSA, PSP, CBS, DLBD or non-degenerative causes of tremor and/or parkinsonism. The study protocol complied with the Helsinki Declaration principles and was approved by the local Institutional Review Board. All patients signed informed consent before participation.

Statistical analysis

The cumulative proportion of diagnoses made over time was modeled by the Kaplan Meier technique. Mean time to diagnosis was calculated for patients with a positive (i.e. change $\geq 25\%$) or negative response to levodopa/carbidopa during the LDC [7,8]. Comparisons were performed by the log-rank test. Multivariate testing was performed by the Cox proportional risk regression for identifying the factors that predicted a more rapid diagnosis. Statistical analysis was performed with R 4.0.1 [13]. The critical alpha value was conventionally set at 0.05.

Results

Five hundred twenty patients were seen between 2009 and 2015. One hundred and eighty-nine cases were excluded due to the absence of detailed information in medical records or lack of follow-up (Figure 1). Data from 326 patients were thus available for analysis and included in this study. There were no differences in age or sex between both groups. Furthermore, the LDC was positive in 46% of the sample of patients included in the study vs. 43% in those that were excluded (chi-sq=0.3; p=0.6).
A FCD of PD was made in 196 of the 326 (60.1%) cases included in this study, and atypical parkinsonism in 46/326 (14.1%). Other FCD were performed in 84/326 (25.8%) cases, as listed in Table 1. Patients with a positive response to LDC had a lower probability of receiving a diagnosis of atypical parkinsonism, suffered more frequently from hyposmia, and showed shorter latencies between the date of first symptoms and the LDC or the FCD (Table 2). Of those patients with a positive response to LDC, a good and sustained chronic response to dopaminergic drugs was present at last follow-up in all patients with a FCD of PD but in none of those with a FCD of non-PD (Table 1). However, a transient response to chronic use of dopaminergic drugs was observed in four non-PD patients (two patients with MSA and two with DLBD).

Overall, FCD was established 7.87±13.2 months after the LDC and 29.4±28.6 months after symptoms onset (Table 2). In the first 6 months after the LDC, a final diagnosis could be reached in 77.5±2.5% of patients, as calculated by the Kaplan Meier method. The time elapsed to reach 90%, 95%, 98%, and 100% of FCD were 20, 33, 50, and 108 months, respectively. Mean time elapsed between the FCD and the last follow-up visit was 40.6 ± 29.9 months. As shown in Figure 2, mean time to FCD was significantly shorter for the PD group compared to the non-PD group (4.1±0.4 months vs. 13.2±1.5 months, $p<0.001$). Mean time to FCD was also shorter in patients with a positive

response to LDC compared to those with a negative one (5.0±0.9 months vs. 10.2±1.0 months, $p<0.01$). Results remained unchanged after repeating all analyses comparing PD patients with those diagnosed with atypical parkinsonism without considering other causes of parkinsonism. Once FCD was established, it remained unchanged at 5 year follow-up visit.

The Cox regression analysis revealed that the time elapsed since the first symptoms onset to the time of the first assessment at our clinic did not affect the time to FCD (Hazard Ratio, 95% Confidence Interval= 0.99, 0.99-1.01, $p=0.22$), while the diagnosis was done faster in those with a lower MDS-UPDRS-III score at baseline (Hazard Ratio [HR] and 95% confidence interval [CI] per unit increase= 1.01, 1.01-1.02, $p<0.01$). Indeed, time to diagnosis was made after 6.3±0.7 months in those with baseline motor scores <20 points (i.e., the median score of the sample) versus 9.3±1.2 months in those with values ≥ to 20 points ($p=0.05$). Shorter times to diagnosis were also associated with positive LDC (HR, 95% CI= 1.35, 1.06-1.72) and a diagnosis of PD (2.07, 1.58-2.70).

Discussion

We could reach a FCD in up to 66% of patients presenting initially with parkinsonism and/or tremor within the first six months after the initial visit. However, the time needed to reach a FCD in the clinical setting in 95% of the patients was 2.75 years. Furthermore, establishing a FCD took up to 9 years in a minority of patients. These time frames are in line with the UKPDSBB and the newer MDS Clinical Diagnostic Criteria for PD [2,3]. Of interest, the time-lapse to a FCD was shorter for the PD group compared to the non-PD group and was also shorter in patients with a positive response

to levodopa in the LDC compared to those with a negative one, and in those patients with baseline MDS-UPDRS-III scores < 20 points. While we did not analyze the predictors of a FCD of PD, our data suggest that lower baseline MDS-UPDRS-III scores might be associated with a higher risk of receiving a final diagnosis of PD. This hypothesis should be tested with an appropriately designed study. It is important to acknowledge, that time to a FCD can be arbitrary in clinical practice as it relies on several aspects, such as the interval between follow-up visits and the experience or confidence level of the neurologists. Taking into account different methodologies across studies, the median time from physician evaluation to PD diagnosis was one to four months (up to 53 months) [14,15], whereas the latency from symptoms onset to diagnosis ranged between 3.9 to 30 months [15,16]. These figures are similar to the ones observed in the current study. In PD patients with pathogenic *Parkin* variants, a diagnostic delay of several years (25.3 ± 17 years) has been particularly reported possibly due to early age at disease onset and a high phenotypic heterogeneity [17,18]. In atypical parkinsonisms, a diagnostic latency of 3.2 ± 2.5 years has been reported in MSA, which was similar than the one observed in CBS (3.2 ± 3.0 years) and in PSP (2.8 ± 2.2 years) [19]. Within CBS and PSP phenotypical subtypes, longer diagnostic latencies were found in the CBS–Alzheimer disease subtype (4.6 ± 3.2 years) and in the PSP-subcortical group, which includes the PSP-parkinsonism and progressive gait freezing subtypes (4.2 ± 3.2 years) [19]. Other studies found similar diagnostic delays in PSP, ranging from 2.4 years [20] to 4.7 years [21], which are similar than those observed in the current study.

Limitations of the current study include i) the retrospective data collection of patients that underwent a prospective diagnostic process; ii) the 36% of excluded patients due to

lack of data or follow-up, despite the fact that this group was similar to the patients included in the study regarding age, sex, and LDC results; iii) the lack of a neuropathological confirmation of the clinical diagnosis [22]; iv) the lack of a group of patients not undergoing LDC, which limited our ability to investigate the diagnostic accuracy of the test; and v) the fact that some patients may have received previous trials with dopaminergic agents before visiting our clinic.

The differential diagnosis of PD is relevant for patient management, and prognosis and is especially challenging at early disease stages despite several attempts made for improving diagnosis by applying different combinations of markers or screening batteries [8, 23-26]. The diagnostic accuracy of clinical diagnosis of PD reported by a systematic review and meta-analysis of 20 studies carried out during the last 25 years, including 11 using pathologic examination as the gold standard, was found to be 79.6% at the initial assessment of movement disorders experts and 83.9% after follow-up [27]. Clear and accurate differentiation between PD and atypical parkinsonism is not easy during early disease stages, because many patients with atypical parkinsonism will not present with the hallmark features, which are also red flags for PD diagnosis [1, 28].

In our study, 30% of clinically defined PD patients showed a negative response to the LDC, but all eventually exhibited a sustained chronic response to dopaminergic therapy at follow-up. Although a substantial initial response to dopaminergic therapy is frequent in PD, it is not universal and its absence does not exclude PD [29]. The role of the LDC in clinical practice as a marker of sustained dopaminergic response [30] is supported by a previous neuropathological study that found a better clinical diagnostic accuracy in patients responsive to dopaminergic therapy [6]. Methodological differences between

previous studies [6, 29] must be considered, especially those referred to the response to dopaminergic therapy during a LDC or after chronic use. The factors that may influence the response to the LDC, causing differences with the long-term dopaminergic response may be the lack of sensitivity of the motor assessment scales in mild cases of parkinsonism, the presence of gastroparesis, or the use of a suboptimal levodopa-carbidopa dose during the test, especially in patients with rest tremor, who may need a subsequent test with crescent doses of apomorphine [30, 31]. According to our results, patients with an acute positive response to levodopa will mostly receive a PD diagnosis, and will have a FCD sooner than those with a negative response. It is expected that in the near future, newer tests or specific diagnostic biomarkers will be available in clinical practice, increasing diagnostic accuracy or substantially reducing the diagnostic latency [32].

In conclusion, in patients with parkinsonism, a FCD could be reached in 95% of the cases within the first 2.75 years after the initial assessment and a LDC, with all cases being diagnosed within the first 9 years. These findings suggest that the follow-up period suggested by the different PD diagnostic criteria are acceptable.

Declaration of interest: None. All authors have approved the final article.

Ethics statement: This study was approved by the local Institutional Review Board and informed consent was obtained. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Funding sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments: None

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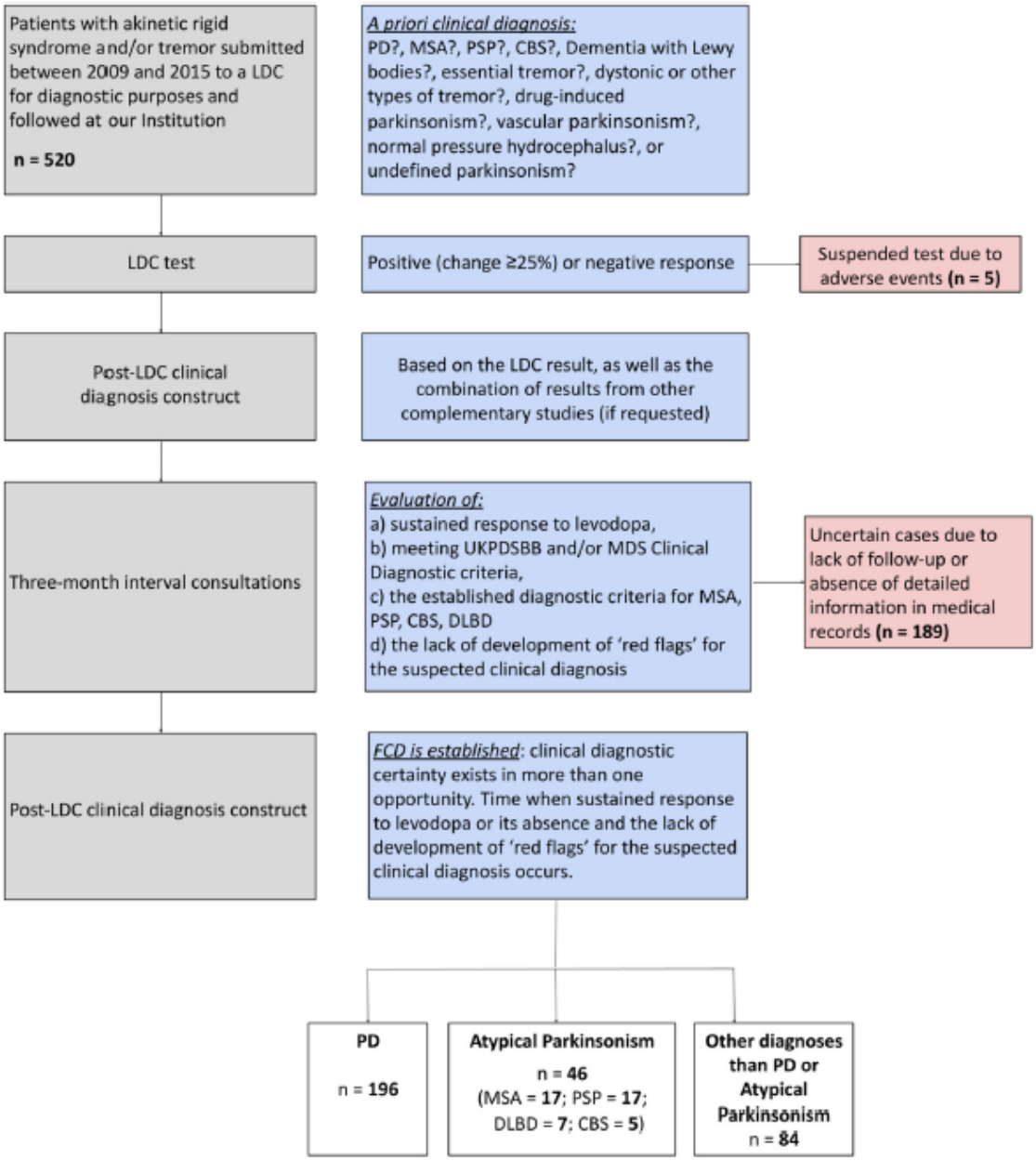

Figure 1. Study flow chart

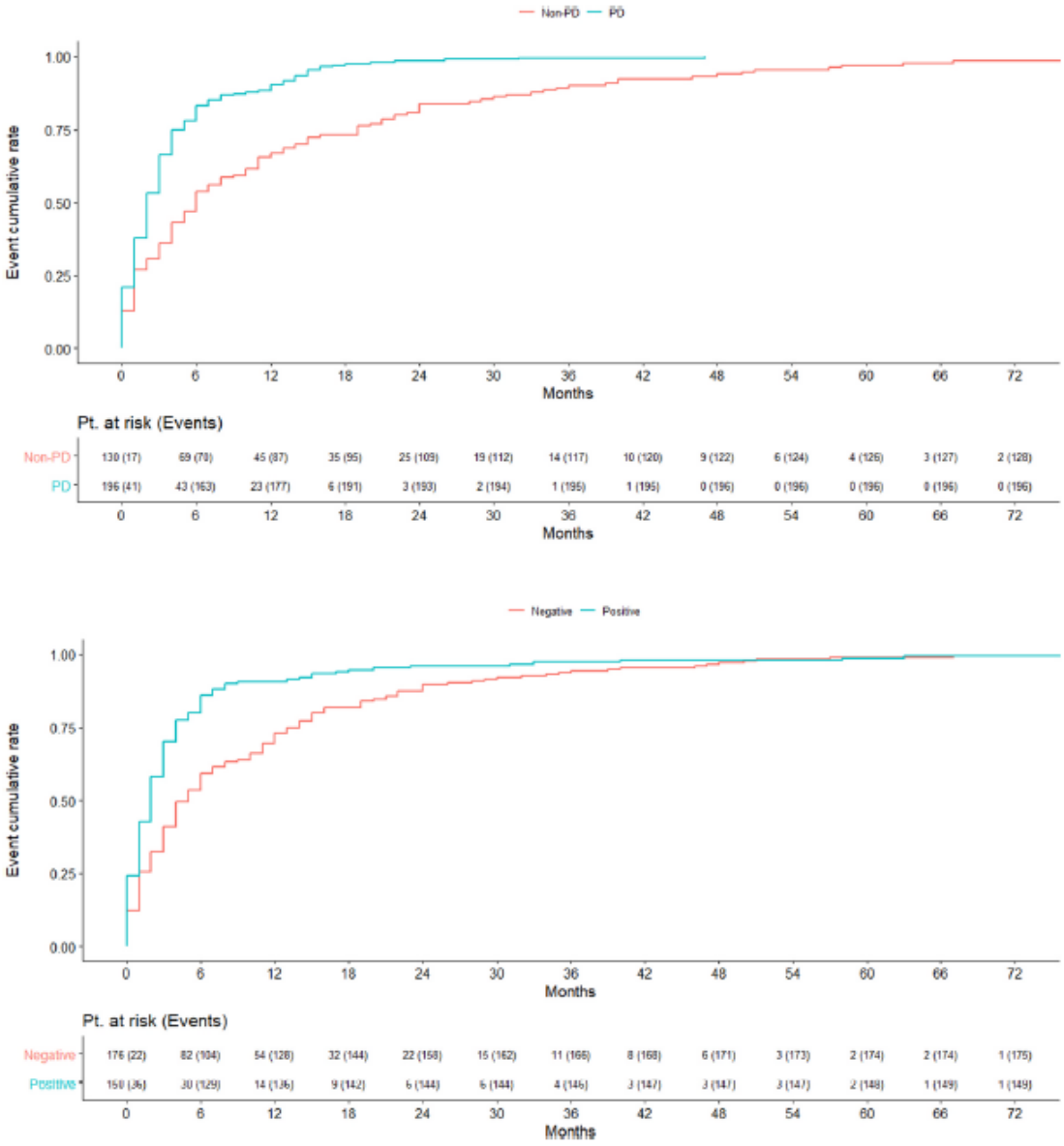

Figure 2. Cumulative proportion of final diagnoses made during the follow-up period, according to the type of diagnosis (top) or the response to levodopa at the LDC (bottom). Curves were sketched until month 72, as there were only two patients at risk after that time point. Event means final clinical diagnosis (FCD).

Table 1
Characteristics of the PD group vs. other causes of parkinsonism.

	PD (n = 196)	Non-PD (n = 130)	P-value
Sex			
Male	119 (60.7%)	70 (53.8%)	**0.26**
Female	77 (39.3%)	60 (46.2%)	
Final Clinical Diagnosis			
PD	196 (60.1%)		**<0.01**
Essential tremor		31 (9.5%)	
MSA		17 (5.2%)	
PSP		17 (5.2%)	
Drug-induced parkinsonism		12 (3.7%)	
Vascular parkinsonism		9 (2.8%)	
Essential tremor plus		8 (2.4%)	
DLBD		7 (2.1%)	
CBS		5 (1.5%)	
NPH		5 (1.5%)	
Dystonic tremor		3 (0.9%)	
AD with parkinsonism		2 (0.6%)	
Functional		2 (0.6%)	
FTD with parkinsonism		1 (0.3%)	
Drug-induced tremor		1 (0.3%)	
CMP		1 (0.3%)	
Fahr's syndrome		1 (0.3%)	
Undetermined		8 (2.5%)	
1st symptoms-LDC latency			
Mean ± SD (mths)	15.3 ± 10.5	29.1 ± 28.1	**<0.01**
Median (P25–P75) (mths)	12.0 (6.0–24.0)	24.0 (12.0–36.0)	
1st symptoms-FCD latency			
Mean ± SD (mths)	19.4 ± 12.4	38.0 ± 34.0	**<0.01**
Median (P25–P75) (mths)	16.0 (10.0–25.75)	28.5 (16.0–46.0)	
LDC-FCD latency			
Mean ± SD (mths)	4.1 ± 6.0	17.4 ± 19.1	**<0.01**
Median (P25–P75) (mths)	2.0 (1.0–4.75)	11.0 (3.0–26.0)	
Test-Lost to F-UP latency			
Mean ± SD (mths)	53.5 ± 29.9	35.6 ± 27.4	**<0.01**
Median (P25–P75) (mths)	57.0 (31.0–75.0)	29.0 (12.0–56.0)	
Olfactory function			
Normosmia	35 (24.5%)	50 (67.6%)	**<0.01**
Hyposmia/Anosmia	108 (75.5%)	24 (32.4%)	
Missing data	53 (27.0%)	56 (43.0%)	
MDS-UPDRS-III before levodopa			
Mean ± SD (mths)	22.3 ± 9.8	23.7 ± 17.9	**0.64**
Median (P25–P75) (mths)	20.5 (16.0–28.0)	20.0 (10.3–32.7)	
Best MDS-UPDRS-III after levodopa			
Mean ± SD (mths)	15.2 ± 7.6	22.2 ± 17.5	**<0.01**
Median (P25–P75) (mths)	14.0 (10.0–19.0)	18.0 (10.0–30.0)	
% reduction in MDS-UPDRS-III after levodopa			
Mean ± SD (mths)	33.8 ± 33.3	14.7 ± 15.7	**<0.01**
Median (P25–P75) (mths)	31.5 (22.0–41.0)	12.0 (0–24.0)	
Good and sustained chronic response to dopaminergic drugs at last follow-up	196 (100%)	0 (0%)	**<0.001**

AD: Alzheimer disease, CMP: Carbon monoxide-induced parkinsonism.
FTD: frontotemporal dementia, LDC: acute levodopa challenge, FCD: final clinical diagnosis; NPH: Normal pressure hydrocephalus.

Table 2
Characteristics of the studied sample according to LDC result.

	Overall *(n=326)*	Negative LDC *(n=176)*	Positive LDC *(n=150)*	P-value
Sex				
Male	189 (58.0%)	99 (56.2%)	90 (60.0%)	0.056
Female	137 (42.0%)	77 (43.8%)	60 (40.0%)	
FCD				
PD	196 (60.1%)	59 (33.5%)	137 (91.3%)	**<0.01**
Essential tremor	31 (9.5%)	29 (16.5%)	2 (1.3%)	
MSA	17 (5.2%)	15 (8.5%)	2 (1.3%)	
PSP	17 (5.2%)	15 (8.5%)	2 (1.3%)	
Drug-induced parkinsonism	12 (3.7%)	12 (6.8%)	0 (0%)	
Vascular parkinsonism	9 (2.8%)	8 (4.5%)	1 (0.7%)	
Essential tremor plus	8 (2.5%)	7 (4.0%)	1 (0.7%)	
DLBD	7 (2.1%)	5 (2.8%)	2 (1.3%)	
CBS	5 (1.5%)	4 (2.3%)	1 (0.7%)	
NPH	5 (1.5%)	5 (2.8%)	0 (0%)	
Dystonic tremor	3 (0.9%)	3 (1.7%)	0 (0%)	
AD with parkinsonism	2 (0.6%)	2 (1.1%)	0 (0%)	
Functional	2 (0.6%)	1 (0.6%)	1 (0.7%)	
FTD with parkinsonism	1 (0.3%)	1 (0.6%)	0 (0%)	
Drug-induced tremor	1 (0.3%)	1 (0.6%)	0 (0%)	
CMP	1 (0.3%)	1 (0.6%)	0 (0%)	
Fahr's syndrome	1 (0.3%)	1 (0.6%)	0 (0%)	
Undetermined	8 (2.5%)	7 (4.0%)	1 (0.7%)	
Main parkinsonian groups				
PD	196 (60.1%)	59 (33,5%)	137 (91,3%)	
Atypical parkinsonism	46 (14.1%)	39 (22.2%)	7 (4.7%)	**<0.01**
Other causes	84 (25.8%)	78 (44,3%)	6 (4.0%)	
1st symptoms-LDC latency				
Mean ± SD (mths)	21.6 ± 23.0	27.2 ± 28.6	15.0 ± 10.6	**<0.01**
Median (P25–P75) (mths)	14.0 (9.00–25.0)	21.5 (12.0–34.5)	12.0 (6.00–23.5)	
1st symptoms-FCD latency				
Mean ± SD (mths)	29.4 ± 28.6	37.4 ± 33.7	20.0 ± 17.1	**<0.01**
Median (P25–P75) (mths)	21.5 (12.0–36.0)	27.5 (17.0–42.0)	15.0 (10.0–25.0)	
LDC-FCD latency				
Mean ± SD (mths)	7.87 ± 13.2	10.2 ± 13.6	5.12 ± 12.3	**<0.01**
Median (P25–P75) (mths)	3.00 (1.00–8.00)	5.00 (1.00–13.3)	2.00 (1.00–4.00)	
Test-Lost to F-UP latency				
Mean ± SD (mths)	48.5 ± 30.4	43.6 ± 28.5	54.2 ± 31.7	**<0.01**
Median (P25–P75) (mths)	52.0 (20.0–71.0)	46.5 (15.8–65.3)	57.0 (28.3–76.8)	
Olfactory function				
Normosmia	85 (26.1%)	55 (31.2%)	30 (20.0%)	**<0.01**
Hyposmia/ Anosmia	132 (40.5%)	47 (26.7%)	85 (56.7%)	
Missing data	109 (33.4%)	74 (42.0%)	35 (23.3%)	
MDS-UPDRS-III before levodopa				
Mean ± SD (mths)	22.6 ± 13.5	22.8 ± 15.7	22.4 ± 10.4	0.79
Median (P25–P75) (mths)	20.0 (13.0–30.0)	19.0 (12.0–31.0)	20.0 (15.3–28.8)	
Best MDS-UPDRS-III after levodopa				
Mean ± SD (mths)	17.4 ± 12.5	20.6 ± 15.0	13.8 ± 7.15	**<0.01**
Median (P25–P75) (mths)	14.0 (10.0–21.8)	17.0 (11.0–28.0)	12.0 (9.00–18.0)	
% reduction in MDS-UPDRS-III after levodopa				
Mean ± SD (mths)	23.0 ± 17.9	9.47 ± 8.69	38.8 ± 11.9	**<0.01**
Median (P25–P75) (mths)	22.2 (8.33–35.0)	8.96 (0–17.8)	35.7 (29.5–45.8)	