The impact of silent vascular brain burden in cognitive impairment in Parkinson's disease

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BACKGROUND AND PURPOSE
White matter hyperintensities (WMHs) detected by magnetic resonance imaging (MRI) of the brain are associated with dementia and cognitive impairment in the general population and in Alzheimer's disease. Their effect in cognitive decline and dementia associated with Parkinson's disease (PD) is still unclear.

METHODS
We studied the relationship between WMHs and cognitive state in 111 patients with PD classified as cognitively normal (n = 39), with a mild cognitive impairment (MCI) (n = 46) or dementia (n = 26), in a cross-sectional and follow-up study. Cognitive state was evaluated with a comprehensive neuropsychological battery, and WMHs were identified in FLAIR and T2-weighted MRI. The burden of WMHs was rated using the Scheltens scale.

RESULTS
No differences in WMHs were found between the three groups in the cross-sectional study. A negative correlation was observed between semantic fluency and the subscore for WMHs in the frontal lobe. Of the 36 non-demented patients re-evaluated after a mean follow-up of 30 months, three patients converted into MCI and 5 into dementia. Progression of periventricular WMHs was associated with an increased conversion to dementia. A marginal association between the increase in total WMHs burden and worsening in the Mini Mental State Examination was encountered.

CONCLUSIONS
White matter hyperintensities do not influence the cognitive status of patients with PD. Frontal WMHs have a negative impact on semantic fluency. Brain vascular burden may have an effect on cognitive impairment in patients with PD as WMHs increase overtime might increase the risk of conversion to dementia. This finding needs further confirmation in larger prospective studies.

KEYWORDS
Dementia, mild cognitive impairment, Parkinson’s disease, silent vascular lesions, white matter hyperintensities

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INTRODUCTION

Dementia occurs in nearly 80% of patients with Parkinson's disease (PD) [1,2]. It has been associated with cortical Lewy bodies (LB), amyloid plaques, neurofibrilary tangles [3], and cholinergic deficit [4]. Cerebrovascular (CV) lesions have been proposed to influence dementia in PD, although this remains to be clearly demonstrated [5–8]. Silent vascular lesions, identified as white matter hyperintensities (WMHs) [9], are associated with dementia in the general population [10–12], and they are thought to aggravate cognitive impairment in Alzheimer's disease (AD) [13] and LB disease [14]. Moreover, WMHs are linked to an in-creased risk of cognitive decline in the elderly and to mild cognitive impairment (MCI) in the general population [15]. The relationship between dementia [16–18] and MCI [16,17,19] in PD and WMHs is controversial. Therefore, we analyzed WMHs in cerebral magnetic resonance images (MRI) from a large cohort of patients with PD using a cross-sectional and longitudinal design, to assess the possible relationship between silent vascular lesions and dementia or MCI in this population.

PATIENTS AND METHODS

The Ethics Committee for Medical Research of the Clinic Universidad de Navarra approved the study, and all participants, or legal representatives, provided their written informed consent.

Patients with PD [21] over 60 years of age and with disease duration of at least 10 years were recruited. Patients with other neurological or psychiatric disorders, severe systemic or vascular disease (stroke, ischaemic heart disease, atherosclerosis, arterial by-pass surgery), or previous cerebral surgery were excluded. Other vascular risk factors obtained by clinical history, interview, and blood tests were recorded but did not constitute exclusion criteria (Table 1). The Hoehn & Yahr scale and the Unified Parkinson's Disease Rating Scale – motor section (UPDRS-III) were used to evaluate disease severity. Patients were classified as showing normal cognition (PDCN), mild cognitive impairment (PD-MCI), or dementia (PDD). DSM-IV criteria were applied to diagnose dementia. MCI was diagnosed in non-demented patients when (i) cognitive decline was reported by either the patient or informant, or observed by the neurologist, but it did not interfere significantly with functional independence of the patient; (ii) the patient scored more than 1.5 standard deviations below the mean for age- and education-appropriate test norms in at least two tests in the neuropsychological battery, either within a single cognitive domain or across different cognitive domains [22].

Parkinson's disease patients without cognitive symptoms and with normal performance in the battery tests were considered as PDCN. For the follow-up study, PDCN and PD-MCI patients were re-evaluated 12–48 months after initial assessment.

The primary aim of this study was to determine the relationship between silent vascular lesions identified as WMHs and cognitive impairment in patients with PD using cross-sectional and longitudinal approaches. A secondary objective was to evaluate how the distribution of WMHs might affect specific cognitive domains.

Neuropsychological evaluations

A trained neuropsychologist performed the following evaluations in patients under the effect of dopaminergic treatment as published elsewhere [23]. Global cognitive function was evaluated using the Mini Mental State Examination (MMSE) and the Blessed Dementia Scale. Daily activities were rated using the Interview for Deterioration in Daily Living in Dementia scale (IDDD). Depression was assessed by the Yesavage Geriatric Depression Rating Scale (GDS). Different cognitive domains were evaluated as follows: verbal episodic memory – Buschke Free and Cued Selective Reminding Test and CERAD word list; visual episodic memory – copy and delayed recall of two simple figures (Massachusetts General Hospital of Boston); language – Boston naming test; attention and executive functions – Raven progressive matrices, semantic "animals" and phonetic "words starting with p" verbal fluency, trail making test A and B and the Stroop test. The tests and the diagnostic criteria were used to determine the cognitive state of each subject.

Magnetic resonance imaging

A brain MRI study was carried out using a 1.5-T MRI scanner MagnetonSP (Siemens, Erlangen, Germany), including FLAIR (TR/TE/TI:8150/125/2500, flip angle 15% matrix size 256 x 179, yielding 10 coronal slices with a slice thickness of 5 mm and in-plane resolution of 0.78 x 0.78 mm), T2- and T1-weighted MPRAGE sequences. Silent vascular brain burden was analyzed as the presence of WMHs, which were defined as hyperintense lesions in both FLAIR and T2-weighted axial MRI sequences. In each patient, the MRI, and the neuropsychological and physical evaluations were performed within the same week. Throughout the study, there was no change in the MRI scanner or in the methodology applied to obtain the images.

White matter hyperintensities rating

White matter hyperintensities were assessed by two trained neurologists blind to the cognitive diagnosis using the semiquantitative visual rating scale of Scheltens [24]. The scale is divided into four subscales rating different brain regions: periventricular hyperintensities (PVH), basal ganglia hyperintensities (BGH), deep white matter, which in this article is called lobar (lobar-WMHs, with its frontal, temporal, parietal, and occipital subscores), and infratentorial. The total score was obtained by the sum of the Scheltens subscores. Rating of WMHs was performed by evaluating the number, size, and localization of the lesions (Data S1).

Statistical analysis

Clinical characteristics and scale scores in the cross-sectional study were analyzed using Fisher's exact test for categorical variables, ANOVA for continuous normally distributed variables, and the Kruskal–Wallis test and a percentile bootstrap method for non-normal distribution. The normal distribution of the residuals and the homoscedasticity were tested. For the WMHs subscales, we applied a multivariate normative comparison [25] followed by a chi-square analysis to test whether the

percentage of cases with higher WMHs scores in cognitively impaired groups differed from an expected percentage of 5% (type I error).

To evaluate how the distribution of WMHs might affect specific cognitive domains, a nonparametric Spearman correlation analysis was performed and adjusted for multiple comparisons with Bonferroni's correction. The significant P-values corrected for multiple comparisons were selected and assessed in a multiple linear regression model which was adjusted for confounding variables, taking each of the cognitive test scores as the dependent variable.

For the prospective study, an association between the change in the cognitive category (cognitively normal, MCI, or dementia) and the increase in the different WMHs Scheltens scores was tested by a Fisher's exact test. A mixed two-factor general linear model was employed to assess the changes in the cognitive results as a function of the baseline WMHs lesion burden or of the increase in the radiological score. A normal distribution of the residuals was determined and Mauchly's test of sphericity was performed. To normalize the data, a power transformation was estimated with the Applied Linear Regression statistics package using the “R” programming language and for the robust methods R.R. The P-values obtained for the different Scheltens subscales were corrected with Bonferroni's correction. Wilcox's robust statistics functions package was used. The statistical analysis was performed using SPSS 15.0 (SPSS15, Inc., Chicago IL, USA) and R 2.11.1. (Development Core Team. R: A language and environment for statistical computing R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

One hundred and eleven patients with PD classified as PDCN (n = 39), PD-MCI (n = 46), or PDD (n = 26) were studied. The general demographic and clinical features are summarized in Table 1. Patients with dementia were older, had higher depression scores, and more severe parkinsonism than the PDCN and PD-MCI groups. In addition, the PDCN group was more educated and showed lower depression scores than the PD-MCI patients. The prevalence of vascular risk factors was evenly distributed among the three groups of patients.

The Scheltens scale scores for the three groups of patients are summarized in Table 2. Owing to shortage of lesions in the parietal and occipital lobes, WMHs in both lobes were merged. The inter-rater and intra-rater agreements were measured using the intra-class correlation coefficient. The resulting values for the different scores ranged from 0.73 to 0.93 for the former and from 0.89 to 0.97 for the later, indicating a high degree of agreement. No difference in the total score or in the subcores was found amongst the three groups of patients (Table 2). The multivariate normative comparison for the subscores found that three patients with dementia and five patients with MCI had higher scores than PDCN patients. However, this number of cases was not significantly different from the expected (P = 0.12 for PD-MCI and P = 0.13 for PDD patients).

The infratentorial score was not considered for correlation studies and for follow-up because of the scarce number of patients presenting WMHs in this region (Table 2). In an ordinal logistic regression controlling for the education level attained, age, UPDRS-

III, and GDS scores, the total WMHs score had no effect on cognitive status (P = 0.58, Nagelkerke R-square of the complete model R = 0.58). None of the WMHs subscores (lobar, PVH, and BGH) were either significant. Furthermore, the relationship between the total score and MMSE was tested in a linear multiple regression model adjusted for age, attained educational level, and GDS score, and no predictive value was found (P = 0.70; R2 = 0.36).

The relationship between the subscores for the distinct lobar regions (frontal, temporal, and parieto-occipital) and the neuropsychological scores for the tests evaluating each cognitive domain was assessed by nonparametric correlations (Table 3). There was a negative correlation between semantic fluency and the frontal score after Bonferroni–Holmes correction was applied (P = 0.01; r = -0.29). To further study this association, the frontal individual scores were grouped into four clinical categories according to the lesion burden (absent = 0, mild = 1–2, moderate = 3–4, and severe = 5–6) and entered in a linear regression model as an independent variable adjusting for confounding factors (educational level, age, and GDS score). In this analysis, semantic fluency was also associated with the frontal score (P = 0.048). Although no linear trend could be found between the four categories and semantic fluency scores (P = 0.057), the category with severe lesion burden had a significantly lower semantic fluency score than the other categories grouped (absent, mild, and moderate) indicating a threshold effect of frontal WMHs burden on semantic fluency (P = 0.008; difference, -2.83 words; 95%CI, -0.75 to -4.85).

LONGITUDINAL STUDY

From the initial cohort of 86 patients with PD, 36 were re-evaluated 12–48 months after the initial assessment (12–24 months, nine patients, 24–36 months, 18 patients; 36–48 months, nine patients; mean = 30.1 months) (Fig. 1). The clinical features of this cohort were not different from those of the non-demented patients excluded from this analysis (n = 49).

Three PDCN patients progressed to MCI and 1 to dementia. Four patients with PD-MCI progressed to dementia. None of the PD-MCI patients normalized to PDCN. In the group followed between 12 and 24 months, no patient showed a change in cognitive diagnosis. In patients followed between 24 and 36 months, one subject progresses from MCI to dementia, and another one from cognitively normal to MCI. After 36–48 months, three patients progressed from MCI to dementia, two from cognitively normal to MCI, and one patient from cognitively normal to dementia. The three groups of patients did not show differences at baseline in MMSE score (P = 0.14) or age (P = 0.67).

A number of patients showed progression of WMHs scores (Table 4). Increasing total, lobar, and BGH subscores of the Scheltens scale were not associated with progression to a more cognitively impaired diagnostic category (MCI or dementia). However, an increase in the PVH subscore was associated with an increased conversion to dementia after adjusting for multiple comparisons (P-value corrected, 0.02). There was no association between an increase in the total WMHs and the change in MMSE performance adjusted for age (P-value for interaction = 0.054). This result was also observed for the lobar-WMHs score, but the effect disappeared after correction for

multiple comparisons (corrected P-value for interaction = 0.13). Changes in semantic verbal fluency with respect to baseline were not significantly affected by an increase in the frontal Scheltens subscore (P = 0.21).

DISCUSSION

The primary finding of this study is that WMHs are not different in the distinct cognitive states of PD patients with no prior relevant vascular disease. However, there is a mild impact of the increment of WMHs (periventricular and total burden) in the progression of cognitive decline. Owing to the small sample size and the excessive attrition of the sample at follow-up, this finding needs to be interpreted with caution and needs further confirmation in larger longitudinal studies. In addition, vascular burden may have a mild effect on certain tasks of executive performance, as witnessed by the negative correlation between semantic fluency and the frontal subscore on the Scheltens scale.

Although cognitive decline in PD is associated with cholinergic degeneration [26], limbic and neocortical LB, AD, and vascular pathology [27], the link between these factors, neuronal loss, and clinical symptoms is ill defined [28]. CV pathology constitutes a risk factor for dementia and cognitive decline in the general population [29], and it also appears to be relevant in AD [13]. However, whilst CV lesions have been proposed to play an important role in PD dementia, this relationship remains to be fully demonstrated [5–8]. Indeed, large neuropathological studies have failed to confirm a significant influence of ischaemic CV alterations on cognitive impairment in patients with PD [5], and cognitive deficiencies appear to be independent of coexisting CV pathology, except when it is severe [6].

Silent vascular lesions, identified as WMHs in MRI images, probably correspond to areas of demyelization and astrocytic gliosis. In addition to the neuronal dysfunction caused by the neurodegenerative process, these white matter pathologies might aggravate the already-defective neuronal connectivity and therefore increase the cognitive dysfunction. Thus, WMHs have been associated with dementia in the general population [10–12, 30–33] and also represents an aggravating factor in cognitive impairment in AD [13] and LB dementia [14]. Moreover, WMHs have been related to a high risk of MCI and a greater decline in global cognitive performance, executive function, and processing speed [15]. In PD, the relationship between WMHs, MCI, and dementia remains unclear [16–19,23,34].

Cross-sectional studies have reported that WMHs burden and cognitive impairment are not associated in PD [16,19,23,34]. Actually, WMHs was not found to contribute to either MCI or attention-executive dysfunction in a cohort of newly diagnosed and untreated patients with PD [19], and WMHs severity was similar in advanced PD patients with dementia, MCI or with no cognitive disability [16].

By contrast, other studies reported more periven-tricular and deep WMHs in demented than in non-demented patients with PD [17,18], and an association between WMHs and lower MMSE scores [18]. These findings should be interpreted with caution, as in addition to the small sample size analyzed, there was no difference in the WMHs

burden in PD patients with dementia when compared to control subjects, whilst non-demented patients with PD exhibited fewer WMHs than controls [18].

We performed a cross-sectional and longitudinal study in a larger cohort of PD patients with more than 10 years of disease evolution, as this profile best represents the PD population at the highest risk of cognitive decline [35]. Although no differences in the WMHs scores in any of the Scheltens subscales were evident between different cognitive states in the cross-sectional study, in what we believe to be the first longitudinal study of its kind, an increment in periventricular WMHs was associated with an increased conversion to dementia. Moreover, a worsening in the MMSE was marginally associated with an increment in the total WMHs burden. Even though the follow-up period is long, our results are limited by the small number of patients, and therefore, larger prospective studies should be carried out.

It has to be admitted that the image acquisition was performed in slice sections 5 mm apart, and very small lesions might have not been captured. However, this applies equally to every patient, and we do not believe it has a significant role in the outcome of this study. In addition, there was no change in the MRI scanner or in the methodology applied to obtain the images throughout the study, and the WMHs burden was evaluated blindly by two trained neurologists with a high inter- and intra-rater agreement.

We also observed a negative correlation between semantic fluency and the frontal score, which persisted in a linear regression model analysis. In keeping with this finding, increased white matter abnormalities in frontal and cingulate regions are associated with executive dysfunction in MCI [36], and impairment in semantic fluency is more severe in non-demented PD patients with significant vascular lesions [37]. Our finding may reflect the dysfunction of the frontostriatal circuit in PD because of degeneration of the dopaminergic system that confers a selective vulnerability for specific executive functions whenever addtional lesions, as silent vascular insults, take place in the frontal lobe.

In conclusion, the first longitudinal study evaluating the role of silent vascular lesions in the cognitive state of patients with PD indicates that although WMHs are not different in the distinct cognitive states, there is a mild impact of the increment of WMHs in the progression of cognitive decline. In addition, frontal WMHs in patients with PD have a negative impact on executive function. Prospective studies with larger cohorts and longer follow-up periods are guaranteed.

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DISCLOSURE OF CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:
Data S1. Scheltens scale: rating of WMHs.
Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

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Table 1. General characteristics of the patients				
	PDCN (n = 39)	**PD-MCI (n = 46)**	**PDD (n = 26)**	**p-values PD-groups**
Age[a]	68.0 (8)	72 (6)	74.0 (6)	0.001[b,c]
PD evolution (years)[d]	13.3 (3.6)	13.4 (4.9)	14 (4.9)	0.959
Gender (%men)	28 (71.8%)	28 (60.9%)	14 (53.8%)	0.314
Levodopa equivalent dose[e] (mg/day)[a]	1000.0 (549)	1105.0 (604)	1000.0 (478)	0.627
UPDRS-III "ON"[a]	12.0 (10.0)	17.0 (12.0)	20.0 (18.0)	0.032[b]
UPDRS-III "OFF"[d]	32.28 (9.35)	34.16 (11.07)	44.61 (11.14)	<0.001[b,c]
Hoehn and Yahr[d]	2.83 (0.81)	2.84 (0.68)	3.6 (0.76)	<0.001[b,c]
GDS[a]	6.0 (6.0)	10.0 (7.0)	14.0 (5.0)	<0.001[b,c,f]
Education (years)[a]	10.0 (10.0)	5 (5.0)	5.0 (0.0)	<0.001[b,c,f]
DM	16.7%	10.3%	15.0%	0.761
Hypertension	60.7%	52.9%	33.3%	0.150
Hypercholesterolemia	16.7%	26.7%	10.5%	0.419
Smoking	10.5%	21.1%	25.5%	0.564

GDS, Yesavage Geriatric Depression Rating Scale; UPDRS-III, Unified Parkinson's Disease Rating Scale-motor section; DM, diabetes mellitus; [a]Median (interquartile range); [b]Significant differences between the PDD and the PDCN groups; [c]Significant differences between the PDD and the PD-MCI groups; [d]Mean (standard deviation); [e]The levodopa equivalent daily dose was calculated for each patient as follows: L-dopa daily dose (mg) = L-dopa (mg) + L-dopa retard (mg)*0.77. In the case of entacapone/tolcapone co-administration, the L-dopa dose was multiplied by 1.33. For dopaminergic agonists, the formula used was Rotigotine (mg)*5 + Ropirinole (mg)* 20 + Pramiprexole (mg)*67 + Cabergoline (mg)*67 + Pergolide (mg)*100 [20]; [f]Significant differences between the PDCN and the PD-MCI groups.

Table 2. Summary of the Scheltens scale scores in the three groups of patients with PD

	Total*	**PVH**	**BGH**	**Lobar-WMHs**	**Frontal**	**Temporal**	**Parieto-occipital**	**Infratentorial**
PDCN	5 (1–11)	0 (0–1)	0 (0–2)	3 (1–8)	2 (1–4)	0 (0–1)	0 (0–2)	0 (0–0)
	85.71%	28.6%	40.5%	84.2%	83.3%	45.23%	47.6%	17.07%
PD-MCI	4.5 (1–17)	0 (0–1.25)	0 (0–3)	4 (1–11.25)	2 (1–6)	0 (0–1)	1 (0–4)	0 (0–0)
	89.13%	41.3%	41.3%	87.3%	86.9%	45.65%	56.5%	17.77%
PDD	6 (3–11)	0 (0–2)	0 (0–1.25)	5 (3–10.25)	4 (1.75–5)	0.5 (0–1)	1 (0–4)	0 (0–0.25)
	88.46%	46.2%	34.6%	89.5%	88.5%	50.00%	57.7%	20.22%

PVH, periventricular hyperintensities; WMHs, white matter hyperintensities; BGH, basal ganglia hyperintensities; *P = 0.62, Uncorrected P-values obtained using a Kruskal–Wallis test; Median (1st and 3rd quartile); % of patients showing WMHs in each cerebral region; Lobar-WMHs: it is the sum of the frontal, temporal, and parieto-occipital white matter lesions; Total: it is the sum of the subscores.

Table 3. Summary of the correlation coefficients obtained between the Scheltens subscores assessing the white matter hyperintensities in the different brain areas and the neuropsychological tests scores evaluating their corresponding cognitive function.

Scheltens subscale	**Cognitive domain**	**Neuropsychological test**	**Nonparametric correlation (corrected P-value)**
Frontal	Attention and executive functions	Raven progressive matrices	0.272
		Semantic verbal fluency[a]	0.01 (r = -0.292)
		Phonetic verbal fluency	1.0
		Trail making A	1.0
		Stroop test color-word direct score	1.0
Temporal	Verbal episodic memory	Free recalls of Buschke	1.0
		CERAD word list	1.0
	Visual episodic memory	Delayed recall of a geometric figure	1.0
	Language	Boston naming test	0.284
Parieto-occipital	Visual episodic memory	Copy of a geometric figure	1.0
		Delayed recall of a geometric figure	1.0
	Attention and executive functions	Raven progressive matrices	1.0
		Semantic verbal fluency[a]	0.185
		Phonetic verbal fluency	1.0
		Trail making A	1.0
		Stroop test color-word direct score	1.0

[a]Verbal fluency in 1 min; Significant results were also encountered for fluency in 30 s; All the P-values are corrected using Bonferroni's correction.

Table 4. Summary of the evolution of the Scheltens scale's scores (unchanged/increased) and of the cognitive state (CN/MCI/D) over the follow-up (12–48 months)

	Scale score follow-up	**Cognitive state follow-up**
Global WMHs Scheltens	Unchanged	7 CN at baseline, 0 converted
n = 36	n = 14	7 MCI at baseline, 2 converted into D
P = 0.68	Increased n = 22	11 CN at baseline, 3 converted into MCI and 1 into D
	3 (2–5)[a]	11 MCI at baseline, 2 converted into D
Lobar-WMHs Scheltens	Unchanged	8 CN at baseline, 0 converted
n = 36	n = 16	8 MCI at baseline, 2 converted into D
P = 1.0	Increased n = 20	10 CN at baseline, 3 converted into MCI and 1 into D
	3 (1–3.5)[a]	10 MCI at baseline, 2 converted into D
PV subscale	Unchanged	12 CN at baseline, 1 converted into D
n = 36	n = 23	11 MCI at baseline, 1 converted into D
P = 0.020	Increased	6 CN at baseline, 3 converted into MCI
	n = 13	7 MCI at baseline, 3 converted into D
	1 (1–2)[a]	
BGH subscale	Unchanged	16 CN at baseline, 3 converted into MCI
n = 36	n = 27	11 MCI at baseline, 2 converted into D
P = 1.0	Increased n = 9	2 CN at baseline, 1 converted into D
	2 (1.5–3)[a]	7 MCI at baseline, 2 converted into D

CN, cognitively normal; MCI, mild cognitive impairment; D, dementia; WMHs, White matter hyperintensities; BG, basal ganglia; [a]Median (interquartilic range) of the increase in the scores; P is the value obtained in the analysis to study whether the increments in the radiological scales predict a change in the cognitive diagnostic category. P-values are corrected for multiple comparisons.

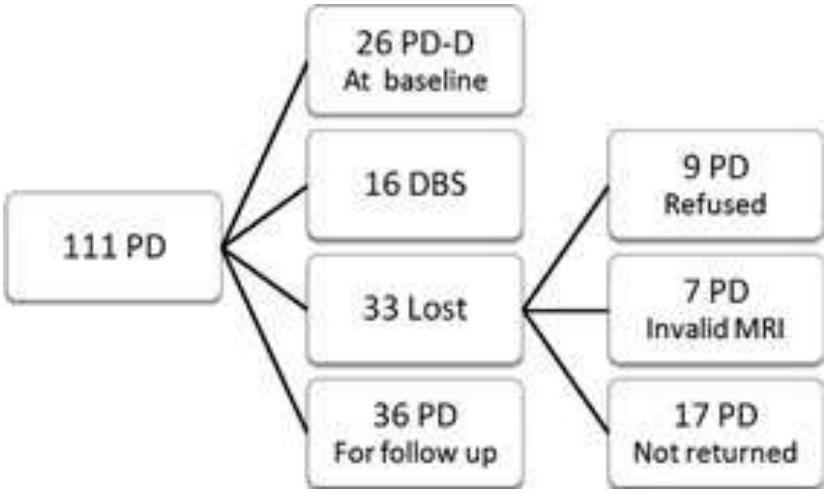

Figure 1. Flowchart of the follow-up of patients with Parkinson's disease from baseline. DBS, deep brain stimulation; PD-D, Parkinson's disease with dementia.