RESEARCH ARTICLE

Longitudinal White Matter Damage Evolution in Parkinson's Disease

CME

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ABSTRACT: Background: White matter hyperintensities (WMHs) have a role in cognitive impairment in normal brain aging, while the effect on Parkinson's disease (PD) progression is still controversial.
Objective: To investigate the longitudinal evolution of micro- and macrostructural damage of cerebral white matter (WM) and its relationship with the clinical picture in PD.
Methods: A total of 154 PD patients underwent clinical, cognitive, and magnetic resonance imaging (MRI) assessment once a year for up to 4 years. Sixty healthy controls underwent the same protocol at baseline. WMHs were identified and total WMH volume was measured. WMHs were also used as exclusion masks to define normal-appearing white matter (NAWM). Using tract-based spatial statistics, diffusion tensor (DT) MRI metrics of whole-brain WM and NAWM were obtained. Linear mixed-effects models defined the longitudinal evolution and association between variables. WM alterations were tested as risk factors of disease progression using linear regression and Cox proportional hazards models.
Results: At baseline, PD patients showed alterations of all DT MRI measures compared to controls. Longitudinally, DT MRI measures did not vary significantly and no association with clinical variables was found. WMH volume changed over time and was associated with impairment in global cognition, executive functions, and language. Baseline WMH volume was a moderate risk factor for progression to mild cognitive impairment.
Conclusions: Our study suggests an association between WMHs and cognitive deterioration in PD, whereas WM microstructural damage is a negligible contributor to clinical deterioration. WMHs assessed by MRI can provide an important tool for monitoring the development of cognitive impairment in PD patients.

Key Words: Parkinson's disease; MRI; normal-appearing white matter; white matter hyperintensity; longitudinal study

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Among the most common white matter (WM) macrostructural alterations, white matter hyperintensities (WMHs) of presumed vascular origin are easily recognized on T2-weighted magnetic resonance imaging (MRI) scans. WMHs are associated with increasing age and cognitive decline in normal aging.[1] In Parkinson's disease (PD), previous evidence from cross-sectional studies suggests an association between total WMH volume and cognitive and/or motor impairment.[2-5] One previous longitudinal MRI study showed no association between motor or cognitive decline and WMH volume increase in PD.[4]

WM microstructural alterations have also been related to neurodegeneration in PD.[6,7] Cross-sectional

studies, using diffusion tensor (DT) MRI, have shown diffuse WM microstructural damage, associated with the degree of motor and cognitive impairment in PD patients.[7-9] Only a few studies investigated the longitudinal evolution of DT MRI alterations, showing a decrease in diffuse fractional anisotropy (FA) and an increase in mean diffusivity (MD) over time,[10-12] reflecting PD severity.[12] However, these studies evaluated the whole brain WM, and did not consider the location and severity of WMHs affecting DT MRI metrics. Only a few reports assessed specifically the involvement of normal-appearing white matter (NAWM) in PD, and they did not find significant alterations in PD patients compared to healthy controls,[13,14] nor any association with clinical features.[14]

Within such a framework, this study aimed to investigate systematically the evolution of both WMHs and NAWM DT MRI alterations and their relationship to the progression of motor and cognitive deficits in a large cohort of PD patients followed up longitudinally for up to 4 years.

Methods

Participants

A cohort of 154 PD patients was prospectively enrolled at the Clinic of Neurology, School of Medicine, University of Belgrade, Belgrade, Serbia as previously described.[15,16] Patients were diagnosed according to the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria,[17] had positive levodopa response, and did not meet diagnostic criteria for vascular parkinsonism.[18] Patients underwent a comprehensive clinical evaluation in ON medication state including clinical, neuropsychological, and MRI assessment at study entry and once a year for at least 1 year and a maximum of 4 years. The study protocol is summarized in Supplementary Figure S1 and extensively described in the Supplementary Material. All 154 patients were included in the study. A cohort of 60 age- and sex- matched healthy controls was recruited from the friends and relatives of the patients and by word of mouth. Healthy controls underwent the same MRI protocol and neuropsychological assessment as PD patients.

The local ethical standards committee on human experimentation approved the study protocol and, prior to study inclusion, all participants provided written informed consent.

Clinical Evaluation

At each visit, an experienced neurologist blinded to the MRI results performed the clinical assessment. Patients were examined in ON state. Demographic and clinical data were obtained using a semi-structured interview described in detail in the Supplementary Material.

Neuropsychological Evaluation

At baseline, patients and healthy controls underwent a comprehensive neuropsychological evaluation within 48 hours of MRI scan. The same test battery protocol was applied at each follow-up visit in PD patients. Evaluations were performed by expert neuropsychologists, blinded to the clinical and MRI data. Details regarding the neuropsychological test battery are reported in the Supplementary Material.

MRI Analysis

Brain MRI scans were acquired at baseline and at each follow-up visit on the same 1.5 T scanner. The Supplementary Material reports the MRI protocol. MRI analysis was performed at the Neuroimaging Research Unit, IRCCS Scientific Institute San Raffaele, Milan, Italy by a single experienced observer, blinded to the subject's identity. The identification of WMHs, DT MRI analysis, and lesion maps were obtained as reported in the Supplementary Material. The framework of MRI analysis is summarized in Supplementary Figure S2. In brief, WMHs, considered to be markers of small vessel disease,[19] were identified on T2-weighted scans using a local thresholding segmentation technique, obtaining a WMH volume at each time point for each subject. Tract-based spatial statistics (TBSS) version 1.2 (http://www.fmrib.ox.ac.uk/fsl/tbss/index.html) was used to perform the multi-subject whole-brain WM DT MRI analysis.[20] Previously detected WMHs were used to create exclusion masks in DT MRI analysis in order to obtain DT MRI metrics of NAWM.

Statistical Analysis

Differences between groups at baseline in sociodemographic, clinical, neuropsychological, and MRI data (ie, DT MRI metrics of whole-brain WM, NAWM) were assessed using independent samples t-test for continuous variables with normal distribution according to the Shapiro–Wilk test and Mann–Whitney U-test for other continuous variables (ie, Unified Parkinson's Disease Rating Scale [UPDRS] and subscores). Categorical variables were compared between groups using Pearson's chi-square test. In each group, DT MRI metrics of whole-brain WM and NAWM were also compared by means of paired samples t-test, to explore the differences in microstructural WM architecture due to the presence of WMHs.

In each group, the correlation between MRI variables and age was assessed by Pearson's correlation analysis. To assess the relationship between structural MRI and clinical/neuropsychological variables at baseline, a partial correlation analysis was performed separately in PD patients and healthy controls, adjusting for age.

In PD patients, changes over time of clinical, neuropsychological, and MRI variables (WMH volume, mean values of whole-brain WM and NAWM FA, MD, axial diffusivity [axD], and radial diffusivity [radD] at each time point) were assessed using linear mixed-effects models with random intercept, using time as a continuous fixed variable. A similar model was applied to investigate the association between the WMH volume changes and the progression of the clinical picture. Such models were adjusted for age, sex, disease duration, and disease severity (UPDRS III score for motor variables and UPDRS I for cognitive variables) at baseline. Analyses involving cognitive data were also adjusted for education, whereas those involving motor variables were also adjusted for levodopa equivalent daily dose (LEDD).

Finally, the capability to predict a clinical outcome using baseline clinical and MRI variables was investigated using linear mixed-effects models with random intercept and Cox proportional hazard models. In the prediction analysis with linear mixed-effects models, global motor (ie, UPDRS total score), and cognitive variables (ie, Mini Mental State Examination [MMSE], Addenbrooke's Cognitive Examination [ACE-R]), as well as UPDRS subscores and domain-specific cognitive performance at the last available time point were considered, separately, as the dependent fixed variable and baseline MRI metrics as independent variables. The models included as fixed variables also age, sex, individual follow-up duration, and baseline disease duration, disease severity (UPDRS III basal score when assessing motor variables, and UPDRS I basal score for cognitive variables), LEDD, and education (only for cognitive variables). The Cox proportional hazard analysis was established to estimate the hazard ratio (HR) and the 95% confidence intervals (95% CIs) of MRI variables at baseline for progression to Hoehn and Yahr (H&Y) score ≥ 3, H&Y score ≥ 4, development of mild cognitive impairment (MCI), or dementia (PD-D), separately. Such models were adjusted for age, sex, disease duration, disease severity (defined by the baseline UPDRS III score for motor variables and UPDRS I for cognitive variables) and LEDD at baseline. The analyses involving cognitive variables were also adjusted for education.

All statistical analyses were performed using R Statistical Software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/) and adjusted for multiple comparisons controlling the false discovery rate (FDR) at the level of 0.05.

Results

Demographic, Clinical, and Cognitive Data at Baseline

The main demographic, clinical, and cognitive data of subjects at baseline are summarized in Table 1. The patient group included 154 PD patients at different disease stages (mean H&Y score = 1.70). Twenty-six patients (17%) had an H&Y score ≥ 3, only one of whom had a score = 4. PD patients and healthy controls were age- and sex-matched, although controls had higher education than patients. Average MMSE and ACE-R total scores, as well as specific cognitive domains, were lower in PD patients relative to controls (P ranging from 0.03 to <0.001), with the exception of language. Ninety-four patients were classified as cognitively normal (PD-CN), and 58 as PD-MCI; two PD patients could not be classified due to incomplete cognitive data.

MRI Measures at Baseline

At baseline, MRI variables representing macroscopic and microscopic WM damage were compared between PD patients and healthy controls (Supplementary Table S1). No differences between groups were found in WMH volume (Table 1), while all the DT MRI metrics differed significantly considering both whole WM and NAWM (P values ranging from 0.005 to <0.001) (Supplementary Figure S3).

In both PD patients and healthy controls, DT MRI metrics were different in NAWM relative to the whole WM (PD: $P < 0.001$; healthy controls: P values ranging from 0.02 to 0.002), showing lower FA and higher MD, axD, and radD values in whole WM. Differences were more prominent in PD patients (Supplementary Table S2).

WMH Distribution

The WMH distribution map of PD patients at baseline (Fig. 1) showed that the probability of lesions occurring in the same spatial location was highest in the frontal and parieto-occipital periventricular areas bilaterally, with a prevalence in the frontal lobes, where the local probability reached a maximum of 15%. The WMH map of the control group showed lesions with similar location but more focused in discrete areas, with the highest lesion probability of 12% in the frontal and peritrigonal regions. Visual comparison of WMH maps showed a more scattered hyperintensity pattern in PD patients, with a diffuse involvement of subcortical WM (Fig. 1).

Baseline Correlation Analysis

In PD patients, age at baseline showed a significant direct correlation with WMH volume ($P = 0.002$), as well as with alterations of NAWM mean DT MRI metrics (P values ranging from 0.01 to <0.001) (Supplementary Table S3). Adjusting for age, the WMH volume of PD patients was directly correlated with UPDRS III tremor subitem ($P = 0.02$), while alterations in NAWM DT MRI metrics correlated with

TABLE 1 *Main sociodemographic and clinical data of Parkinson's disease patients and healthy controls at baseline*

Variable	PD	Healthy controls	*P* value
N	154	60	–
Age (y)	61.58 (7.95)	61.78 (8.98)	0.88
Education (y)	12.46 (2.59)	13.52 (2.57)	0.01
Disease duration (y)	4.95 (4.84)	–	–
Age at onset (y)	56.64 (8.26)	–	–
Sex (M/F)	91/63	29/31	0.17
UPDRS I	4.12 (3.15)	–	–
UPDRS II	9.21 (5.53)	–	–
UPDRS III	28.59 (15.81)	–	–
UPDRS IV	1.17 (1.88)	–	–
UPDRS total score	43.09 (21.51)	–	–
Hoehn & Yahr stage	1.70 (0.81)	–	–
Tremor	4.31 (4.78)	–	–
Postural and gait disturbances	4.70 (3.87)	–	–
Axial symptoms	5.11 (3.28)	–	–
Rigidity	20.10 (8.11)	–	–
Bradykinesia	7.59 (4.04)	–	–
LEDD (mg)	512.61 (414.58)	–	–
FoG-Q score	2.86 (3.82)	–	–
Cognitive status at baseline (normal/MCI)	94/58	60/0	–
MMSE	28.40 (1.59)	29.62 (0.72)	<0.001
ACE-R	89.52 (7.21)	96.28 (3.00)	<0.001
Memory	−0.34 (2.26)	1.21 (2.345)	0.001
Executive functions	−0.57 (3.12)	1.10 (2.29)	0.001
Language	−0.04 (1.45)	0.15 (0.90)	0.27
Fluency	−0.07 (1.07)	0.21 (0.71)	0.03
Visuospatial functions	−0.27 (1.64)	0.88 (1.02)	<0.001
Baseline WMH volume (mL)	484.53 (74.34)	388.89 (62.82)	0.22
1-y WMH volume (mL)	592.05 (88.42)	–	–
2-y WMH volume (mL)	624.17 (81.57)	–	–
3-y WMH volume (mL)	587.87 (87.52)	–	–
4-y WMH volume (mL)	871.77 (121.7)	–	–

Data are expressed as mean value (standard deviation) or frequency. Raw scores from patients' neuropsychological tests were converted to *z* scores based on mean and standard deviation of the correspondent score derived from our control group. Comparisons were made using independent samples t-test and Mann–Whitney U-test for continuous variables, as appropriate. Categorical variables were compared using F-Fisher's exact test.

Abbreviations: PD, Parkinson's disease; y, year; M, male; F, female; UPDRS, Unified Parkinson's Disease Rating Scale; LEDD, levodopa equivalent daily dose; FoG-Q, Freezing of Gait Questionnaire; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; ACE-R, Addenbrooke's Cognitive Examination Revised; WMH, white matter hyperintensities.

H&Y stage (FA and radD, $P = 0.04$ and $P = 0.03$, respectively), LEDD (FA, $P = 0.03$), UPDRS III tremor subitem (axD, $P = 0.04$), and memory performance (MD and radD, $P = 0.03$) (Supplementary Tables S3 and S4). In healthy controls, WMH volume and alterations in NAWM mean FA, MD, and radD were directly correlated with age (*P* values ranging from 0.01 to 0.001, Supplementary Table S5).

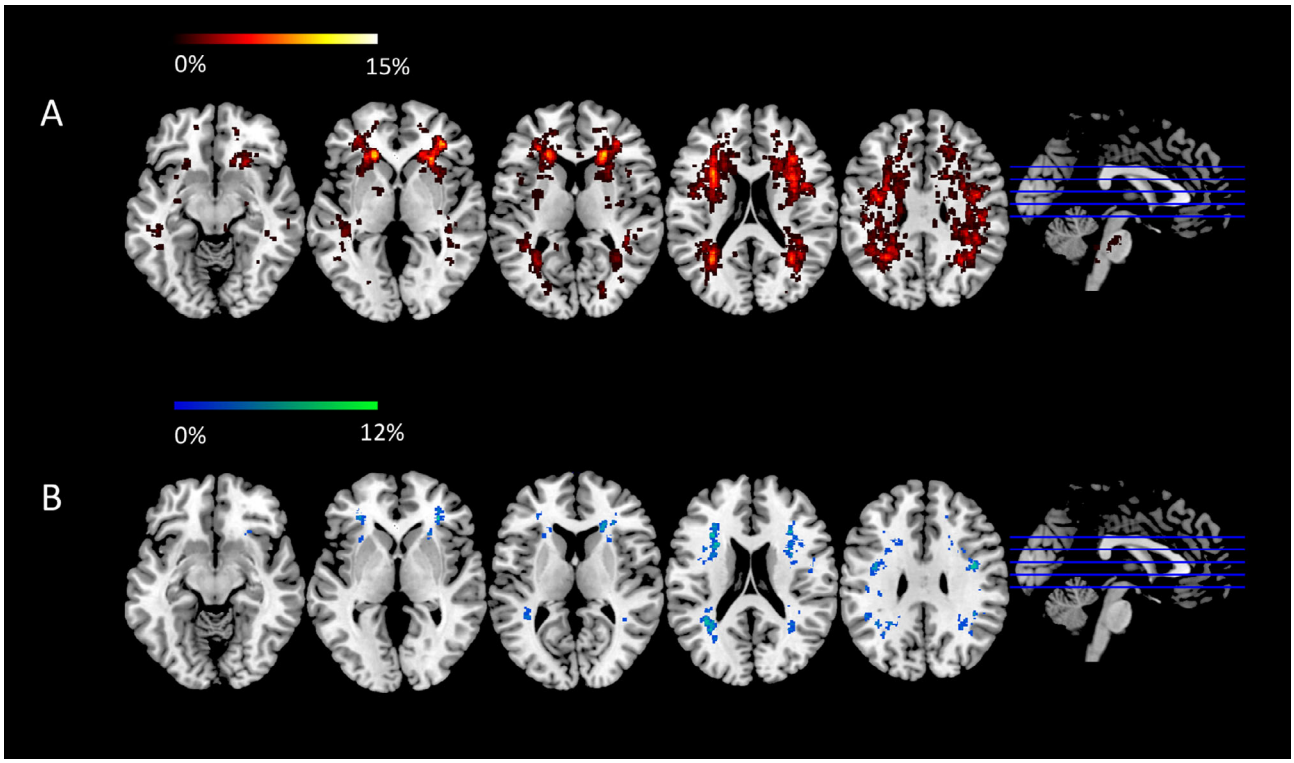

FIG. 1. Probability lesion maps at baseline. The figure shows the probability lesion maps of white matter hyperintensities in both Parkinson's disease (**A**) and healthy control (**B**) groups. The lesion probability is encoded by color intensity. [Color figure can be viewed at wileyonlinelibrary.com]

Longitudinal Clinical, Neuropsychological, and MRI Findings

PD patients showed a progressive worsening over follow-up in terms of global clinical (UPDRS total score and subscores) and cognitive scores (MMSE, ACE-R – P values <0.001) (Table 2). Moreover, all UPDRS III subitems, with the exclusion of tremor, showed a significant worsening, while the progression of cognitive impairment was more prominent regarding executive and visuospatial functions, as shown by the corresponding composite scores (Table 2). Regarding disease stage, 26 patients with baseline H&Y ≤ 2 progressed to H&Y disease stage≥3 (20%), and two patients initially staged as H&Y = 3 progressed to H&Y ≥ 4 (8%). None of the initially H&Y ≤ 2 patients progressed to H&Y ≥ 4. At the end of the follow-up, 41 patients were classified as H&Y ≥ 3 (27%) and 3 patients ≥4 (2%). During follow-up, 37 PD-CN subjects converted to PD-MCI (39%) and 24 PD patients initially classified as PD-MCI converted to PD-dementia (PD-D) (41%). None of the initially PD-CN patients converted to PD-D during the observation period. At the end of the follow-up, 57 PD subjects were cognitively normal (37%), while 73 were classified as PD-MCI (47%) and 24 as PD-D (16%).

WMH volume increased significantly over time ($P < 0.001$). By contrast, the evolution of DT MRI metrics in both the whole WM and NAWM did not show a significant progression over time (Table 2).

Longitudinal Association Analysis

According to the observation of increased WMH volume over time in PD patients, its association with clinical evolution was investigated longitudinally (Fig. 2, Supplementary Table S6). The global cognitive worsening (UPDRS I, $P = 0.01$; MMSE, $P = 0.02$; ACE-R, $P = 0.003$) was associated with WMH volume increase over time. Regarding the evaluation of different cognitive domains, the worsening in executive functions ($P = 0.01$) and language ($P = 0.03$) was associated with WMH volume increase. No other associations were observed.

Prediction Analysis

WMH volume at baseline predicted UPDRS I score at the last follow-up visit ($\beta = 1.48$; $P = 0.004$). No significant associations were found between any other MRI variable at baseline and clinical and cognitive variables at the end of follow-up (Supplementary Tables S7 and S8).

In the Cox proportional hazards analysis (log rank<0.001, Supplementary Table S9), higher UPDRS III score at baseline showed a negative influence on the

TABLE 2 *Longitudinal evolution of motor, cognitive, and magnetic resonance imaging variables in Parkinson's disease patients*

Parameter	Slope	SE	*P* value
Motor variables			
UPDRS I	0.0027	0.0003	<0.001
UPDRS II	0.0049	0.0004	<0.001
UPDRS III	0.0082	0.0007	<0.001
UPDRS IV	0.00048	0.0001	<0.001
UPDRS total score	0.01658	0.0011	<0.001
Tremor	0.0003	0.0002	0.38
Postural and gait disturbances	0.0010	0.0002	<0.001
Axial symptoms	0.0014	0.0001	<0.001
Rigidity	0.0042	0.0004	<0.001
Bradykinesia	0.0010	0.0002	<0.001
Cognitive variables			
MMSE	−0.0011	0.0001	<0.001
ACE-R	−0.0024	0.0005	<0.001
Memory	−0.0004	0.0031	0.89
Executive functions	−0.0034	0.0004	<0.001
Language	−0.0008	0.0008	0.26
Fluency	−0.0005	0.0007	0.53
Visuospatial functions	−0.0034	0.0004	<0.001
MRI variables			
WMH volume	0.0002	0.0001	<0.001
Whole WM mean FA	0.0000003	0.0001	0.53
Whole WM mean MD	−0.0000039	0.0001	0.11
Whole WM mean axD	−0.0000077	0.0001	0.12
Whole WM mean radD	−0.0000020	0.0001	0.14
NAWM mean FA	0.00000003	0.0001	0.54
NAWM mean MD	−0.00000004	0.0001	0.57
NAWM mean axD	−0.00000008	0.0001	0.54
NAWM mean radD	−0.00000002	0.0001	0.59

Longitudinal evolution of variables are described by slope and standard error (SE) of the linear mixed-effects model with random intercept. *P* values <0.05 are considered statistically significant after false discovery rate correction.
Abbreviations: SE, standard error; UPDRS, Unified Parkinson's Disease Rating Scale; MMSE, Mini Mental State Examination; ACE-R, Addenbrooke's Cognitive Examination Revised; MRI, magnetic resonance imaging; WMH, white matter hyperintensities; WM, white matter; FA, fractional anisotropy; MD, mean diffusivity; axD, axial diffusivity; radD, radial diffusivity; NAWM, normal-appearing white matter.

4-year progression to H&Y ≥ 3 (HR 1.09, 95% CI 1.06–1.12), similar to longer disease duration (HR 1.11, 95% CI 1.03–1.20). Greater WMH volume at baseline showed an independent, negative influence on the progression from normal cognition to MCI during the 4-year follow-up (HR 1.51, 95% CI 1.14–2.00) (Fig. 3). Moreover, also higher age (HR 1.08, 95% CI 1.05–1.11) showed a negative influence on progression to MCI status, while male sex (HR 0.50, 95% CI 0.32–0.80) and higher education level (HR 0.73, 95% CI 0.67–0.79) were protective factors. The other variables at baseline (including DT MRI measures) did not show any influence on progression to H&Y ≥ 3 and conversion to MCI. No significant predictors of progression to H&Y ≥ 4 and dementia (log rank = 0.20) were identified.

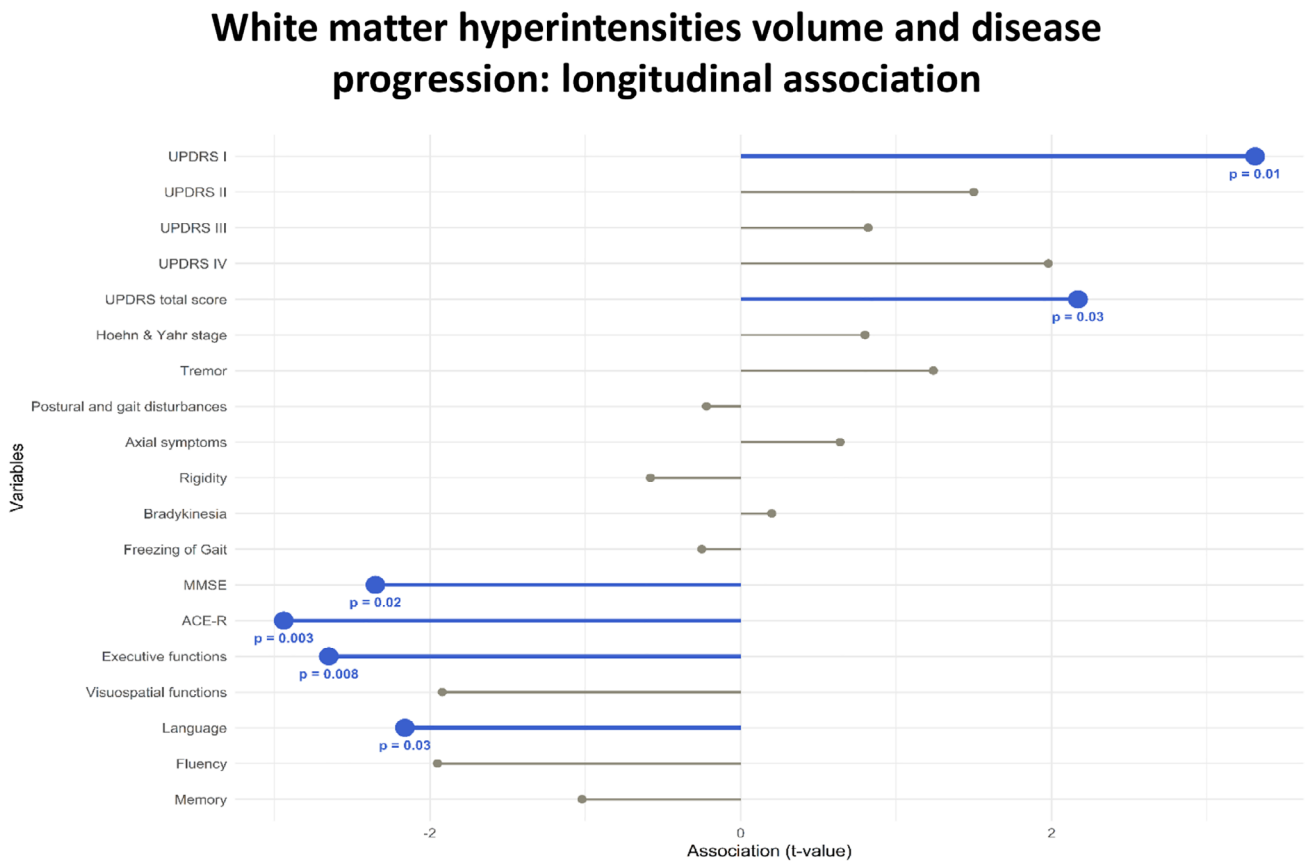

FIG. 2. Lollipop chart showing longitudinal association analysis between white matter hyperintensities volume, clinical, and cognitive variables. *P* values <0.05 are considered statistically significant after false discovery rate correction. UPDRS, Unified Parkinson's Disease Rating Scale; MMSE, Mini Mental State Examination; ACE-R, Addenbrooke's Cognitive Examination – Revised. [Color figure can be viewed at wileyonlinelibrary.com]

Discussion

Our study investigated the longitudinal evolution of WM macro- and microstructural damage in a large cohort of well-characterized PD patients, as well as the relationship between MRI measures and the evolution of the motor and cognitive clinical picture. Increased WMH volume over time in PD patients was associated with the progression of global cognitive impairment and worsening in specific cognitive domains, including executive functions and language. Moreover, WMH burden at baseline predicted cognitive worsening at the end of the follow-up (as measured by the UPDRS I score) and acted as a moderate risk factor for the conversion from normal cognition to MCI in PD patients. Although NAWM DT MRI alterations were found at baseline in PD patients relative to healthy controls, they did not show a significant progression over follow-up and were not associated with longitudinal changes in motor or cognitive impairment. The results of this study offer interesting insights regarding the influence of WM alterations over the clinical evolution of idiopathic PD.

At baseline, our results showed the presence of extensive damage in WM, which impacted motor and cognitive functions. Despite a slightly more diffuse pattern of damage being observed in PD patients on visual inspection of WMH distribution maps, no differences in whole-brain WMH volume were found when comparing PD patients with the age- and sex-matched group of healthy controls. This observation is in agreement with previous studies that support the view that the total WMH volume is not significantly higher in PD patients compared to controls.[4,21] On the contrary, our study showed significant differences in NAWM DT MRI metrics when comparing PD patients and healthy controls, highlighting microstructural alterations of WM in PD extending beyond WMHs. The comparison between our findings and previous studies investigating NAWM in PD[13,14] is hampered by the different samples and methodological approaches (eg, average NAWM skeleton vs. regional DT MRI analysis[13,14]).

After adjusting for the effect of age, the correlation analysis of baseline MRI measures showed that DT MRI metrics were mainly associated with disease stage, the presence of tremor, and memory impairment, whereas WMH volume was significantly correlated with the degree of tremor. Taken together with previous studies,[2,3,8,9,12] our results expand the notion that

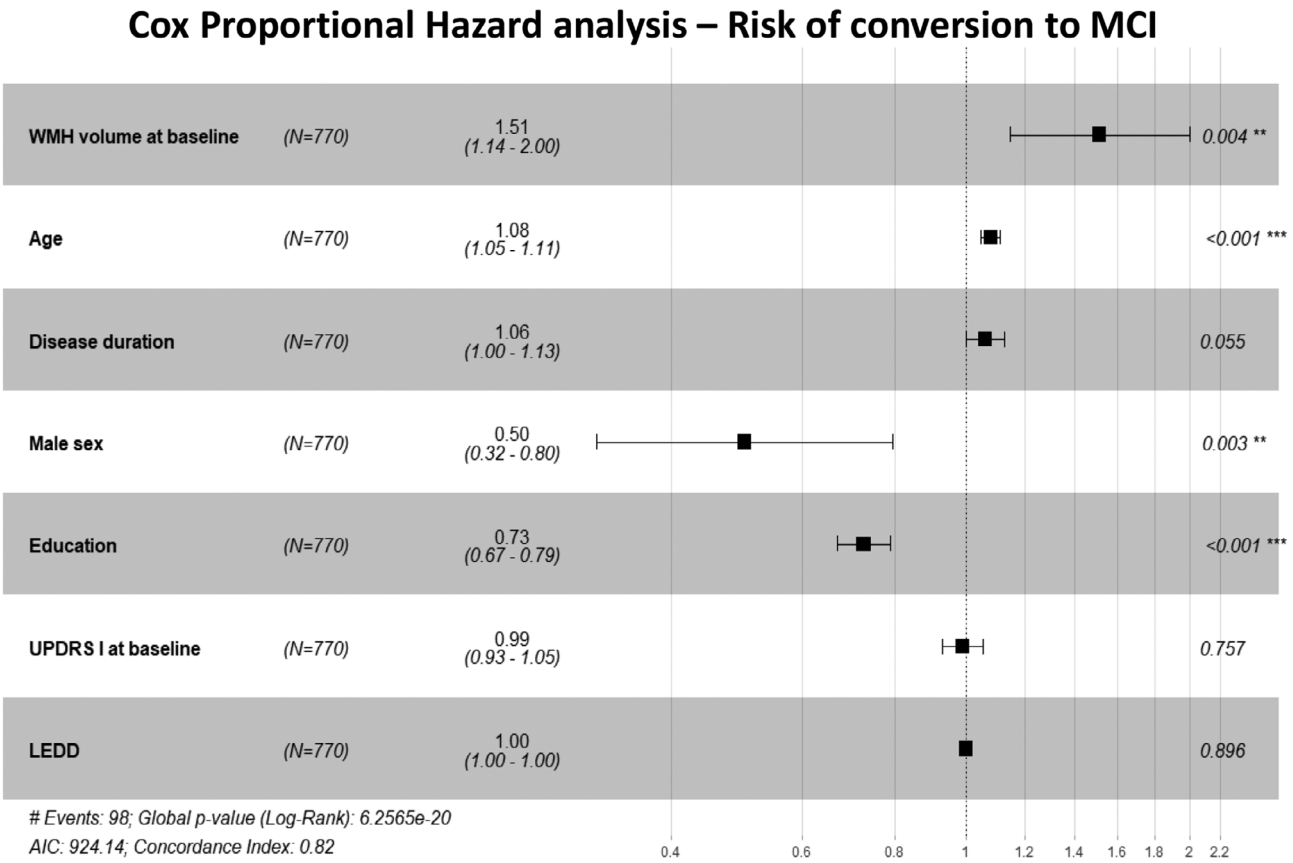

FIG. 3. Cox proportional hazard analysis. The figure shows the forest plot of the Cox proportional hazard analysis that describes the progression to mild cognitive impairment (MCI) status. Among the considered covariates, the total volume of white matter hyperintensities at baseline appears to be a relevant risk factor. WMH, white matter hyperintensities; UPDRS, Unified Parkinson's Disease Rating Scale; LEDD, levodopa equivalent daily dose.

WM micro- and macrostructural alterations contribute to motor features, alongside the well-known influence on cognitive impairment.[2,3,8,9,12]

PD patients experienced a worsening of both motor and non-motor symptoms over time, with a significant progression of UPDRS and related subscores, as well as global cognitive test scores, and executive and visuospatial functions, as expected in consideration of PD's natural course.[22-27] The longitudinal analysis of WMH volume showed a significant progression over time, which was associated with the cognitive decline, especially regarding executive functions and language. By contrast, WMH volume increase was not correlated with the worsening of motor variables. Most previous longitudinal studies investigating the relevance of WMHs on motor and cognitive progression in PD considered only WMHs at baseline, and did not assess their changes over time.[2,3,5,28] To date, only one study investigated the relationship between changes in WMH burden and clinical picture in a small cohort of PD patients with a 18-month follow-up, showing no association between WMH volume changes and cognitive progression, even though WMH increase over time showed a significant interaction with UPDRS motor subscores.[4] The larger sample and the longer clinical and MRI follow-up in our study may explain the different findings. Interestingly, in our cohort, the affected domains that showed a significant association with WMH volume increase were the ones usually most affected in vascular cognitive impairment.[29,30] This observation suggests an additional negative influence of WMH burden on the natural course of PD-related cognitive impairment, with a more prominent impairment in executive and language functions.

The longitudinal analysis of DT MRI metrics of the whole WM and NAWM did not show significant changes in PD patients. The few previous longitudinal studies assessing the evolution of WM microstructural damage in PD patients adopted a regional approach, using either TBSS or regions of interest.[10,12,31] Increased MD was associated with progressive motor impairment, while reduced FA was associated with motor impairment and cognitive decline in PD-CN and PD-MCI.[10,12,31] Thus, although we cannot exclude that additional microstructural WM damage has occurred in our patients, we may conclude that either such a progression was not diffuse in our sample or mean NAWM DT MRI metrics are not the appropriate measures to detect such changes.

Interestingly, the longitudinal increase of WMH volume was not accompanied by a comparable worsening of DT MRI alterations in PD patients. Therefore, we suppose that DT MRI abnormalities and WMH increase may follow different patterns of evolution, with an earlier development of DT MRI alterations conferring vulnerability to later accumulation of WMH burden. This supposition is in line with a previous study that showed, in cognitively normal elderly individuals, the association between baseline DT MRI alterations with the subsequent WMH growth over time.[32] However, future investigation will be necessary to fully clarify these relationships.

Baseline DT MRI variables were unable to predict the 4-year motor and cognitive outcome, whereas baseline WMH volume successfully predicted the UPDRS I score at the end of the follow-up and acted as a moderate risk factor for conversion from PD-CN to PD-MCI. Similarly, in a previous study, baseline WMH volume was a marker of cognitive decline over 4 years, predicting the Montreal Cognitive Assessment score and cognitive status (ie, normal cognition, MCI, or dementia).[33] Another study reported the capability of WMH burden at baseline to predict conversion to PD-D, although such a finding did not survive statistical correction for confounders.[5] A third study showed a negative impact of higher baseline WMH volume on cognition over a mean follow-up time of 29.8 months.[28]

The added value of our study is the quantification of the importance of variables as risk factor of progression. Using a multivariate model, we showed the importance of baseline WMH volume as a moderate independent risk factor (HR = 1.51) of conversion to PD-MCI, with a prominent role compared to the classical risk factors of disease progression, such as age. In addition, our analysis showed a protective role of education and female sex. As expected, higher levels of education were associated with better cognitive performance and a slowing in cognitive decline.[34] The role of sex in progression to cognitive impairment is unclear, even though our result of the protective effect of male sex is unexpected. In fact, in PD patients, an association between male sex and cognitive impairment has been generally observed, as reported in a recent meta-analysis of 15 studies.[35] However, it should be considered that such influence was mild, compared to other factors (eg, age, degree of motor impairment, education, and so on).[35]

UPDRS III score at baseline acted as a risk factor for the progression to advanced motor disease stages. These results are concordant with previous studies that associated disease severity at baseline with motor progression.[36] As expected, our results confirmed that patients with more severe baseline impairment continue to be more impaired later in the disease course and are more likely to progress to advanced disease stages.[36]

As is evident, the relationship between WMHs and motor and cognitive impairment in PD still remains unclear, even though a role in disease progression may be supposed. It is unlikely that WMHs represent an epiphenomenon of abnormal protein aggregates deposition, rather than vascular risk factor-related small-vessel disease. In fact, pathological studies found evidence of an association between WMHs and loss of vascular integrity, indicating a vascular origin for these lesions.[37] Interestingly, a previous study showed a link between low levels of amyloid beta in the cerebrospinal fluid, WMHs, and dementia in PD.[38] This observation supports the hypothesis that vascular pathology associated with WMHs might lead to a reduction in amyloid clearance and subsequent accumulation and deposition in brain tissue.[39] A similar interaction between α-synuclein deposition and vascular damage might represent a pathophysiological mechanism capable of explaining the synergic or additive role of vascular damage on disease progression in PD.

Our study is not without limitations. First, our data lack follow up of the healthy control cohort, therefore we were unable to compare impairment in PD with normal aging. Moreover, we focused on the role of WM alteration on PD progression without taking into account other factors related to damage (ie, modifiable vascular risk factors). Moreover, we assessed WMH volume and mean DT MRI metrics of the whole-brain WM skeleton without regional analysis. Finally, we assessed WMHs on 1.5 T scans, even though higher scan fields allow a more accurate identification.

In conclusion, we demonstrated in a large sample of PD patients that the increase over time of WMH volume is associated with cognitive deterioration, and WMH volume at baseline represents a moderate risk factor of progression to MCI. Therefore, the progression of macroscopic WM damage in PD may represent a quantifiable biomarker with a key prognostic value. Based on the present findings, we strongly support the need for prevention and treatment of vascular risk factors that might aggravate WMH burden in patients with PD, in order to avoid a faster disease evolution.

Data Availability Statement

The dataset used and analyzed during the current study will be made available by the corresponding author upon request to qualified researchers (i.e., affiliated to a university or research institution/hospital).

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.