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White matter hyperintensities are not associated with cognitive decline in early Parkinson's disease – The DeNoPa cohort

Uta Hanning[a,b,*], Anja Teuber[b], Elisabeth Lang[c], Claudia Trenkwalder[c], Brit Mollenhauer[c,d,1], Heike Minnerup[b,1]

[a] Department of Diagnostic and Interventional Neuroradiology, University Medical Center Hamburg-Eppendorf, D-20246, Hamburg, Germany
[b] Institute of Epidemiology and Social Medicine, University of Muenster, Albert-Schweitzer-Campus 1, D-48149, Muenster, Germany
[c] Paracelsus-Elena-Klinik, Klinikstraße 16, D-34119, Kassel, Germany
[d] University Medical Center Göttingen, Department of Neurology (BM), Robert-Koch Straße 40, D-37075, Göttingen, Germany

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ABSTRACT

Background: Small vessel disease and white matter hyperintensities (WMH) as its surrogate marker are known to predict cognitive decline in the elderly. However, the influence of vascular lesions on cognitive impairment in Parkinson's disease (PD) has been discussed controversial so far. The Aim of this study was to evaluate the predictive role of volume and location of white matter hyperintensities (WMH) on cognitive decline in de novo PD patients.

Methods: 108 diagnosed drug-naïve PD patients (64 ± 9 years, 38% women) from the DeNoPa Cohort underwent extensive neuropsychological testing with re-testing in 24-month later. Movement Disorder Society criteria for the classification of mild cognitive impairment (MCI) and dementia in PD were applied. Participants that declined from normal cognition or MCI at baseline to MCI or dementia at 24-month follow-up (FU) or from MCI to dementia at 24-month FU were defined as "converters". Subjects with stable cognitive level or improved cognitive status were classified as "non-converters". Magnetic resonance imaging (MRI) was performed, and the extent of WMH was assessed as global volume and as WMH load within cholinergic pathways using the Cholinergic Pathways Hyperintensities Scale. We compared Parkinson's disease subjects with age-matched, neurologically healthy controls.

Results: At total of 29 (27%) patients met the criteria for MCI at baseline, whereas 79 (73%) patients had no cognitive impairment. During the 24-month FU 33 patients showed cognitive decline ("converter") compared to 75 "non-converters". Multivariable logistic regression revealed no significant differences between "cognitively impaired" and "cognitively non-impaired" patients and participants of the control group at baseline or between "converter" and "non-converter" regarding the extent of WMH globally or within cholinergic pathways.

Conclusions: We could not identify global or localized WMH load as predictive markers of cognitive decline in de novo PD patients indicating that cerebral small vessel disease is not a critical modifier of cognitive function in early PD.

1. Introduction

Parkinson's disease (PD) affects up to 2% of individuals aged 65 years and older and is the second most frequent chronic neurodegenerative disorder [1]. The disruption of different neurotransmitter systems, including cholinergic and dopaminergic pathways, leads to various non-motor and motor-symptoms [2]. Cognitive impairment is one of the most disabling non-motor symptoms of PD with a prevalence of 20–35% even in early stages of the disease. According to a prospective study, nearly 80% of newly diagnosed PD-patients develop dementia within 20 years [3]. In spite of the high prevalence of cognitive impairment in PD its pathophysiology is not well understood, but dopaminergic and cholinergic denervation are discussed as potential contributors to cognitive dysfunction in PD [4]. Longitudinal imaging studies could offer more insights into the pathophysiology of cognitive impairment in PD and might come up with potential imaging

* Corresponding author. Department of Diagnostic and Interventional Neuroradiology, University Medical Center Hamburg-Eppendorf, D-20246, Hamburg, Germany.
E-mail address: u.hanning@uke.de (U. Hanning).
[1] Both senior authors contributed equally.

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biomarkers for cognitive decline in PD patients. Small vessel disease and white matter hyperintensities (WMH) as its surrogate marker are known to predict cognitive decline in the eldery [5]. However, in PD the influence of vascular lesions on cognitive impairment is discussed controversial in the literature with few studies indicating a positive relationship [6–10] between cognitive impairment and WMH load while other studies report absence of a significant association [11]. The discrepancies might partly be due to the differences in the procedures of scoring WMH on MRI and the application of different MRI scanners with different field strength. Other important factors are the varying assessment of cognitive function and the differing stages of Parkinson's Disease of the included patients in other studies. Moreover, besides global WMH volume the specific location of WMH might be more precise in predicting cognitive decline in PD. The cholinergic Pathway Hyperintensities scale (CHIPS) [12], a visual rating scale adapted from immunohistochemical tracings of the cholinergic pathway, has been associated with cognitive impairment and cognitive decline in Parkinson's disease in two studies [13,14]. However, both studies did not include de novo PD patients. In the present study, we therefore evaluated the ability of global WMH volume and the strategic CHIPS score to predict cognitive decline in 108 drug-naïve de novo PD participants and further compare it to 104 healthy controls. All patients and controls were participants of the DeNoPa Study, a prospective single-centre cohort study [15].

2. Material and methods

2.1. DeNoPa study

The DeNoPa cohort was recruited between 2009 and 2011 at the Paracelsus-Elena-Klinik, Kassel, Germany. The study comprises 159 Parkinson's disease subjects (PD) and 110 non-PD controls (NC) matched by frequency according to age, sex and education (Fig. 1). The study design, clinical baseline characteristics, inclusion and exclusion criteria have been recently described [15]. The first of the bi-annually planned longitudinal follow-ups was completed in December 2013 by 147 Parkinson's disease subjects and 107 controls [16].

2.2. Study participants

Various demographic and clinical parameters, including comorbidities, medication and standardised neurological examinations were assessed in those that returned for the first follow-up [15]. The neurological examination included the Movement Disorder Society-revised Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part I to VI [17] as well as Hoehn and Yahr staging [18]. For the current analyses only participants with complete MR images at baseline and with complete neuropsychological tests at baseline and follow up were included. Patients with other neurological diseases (including non-PD dementia), missing or incomplete baseline (BL)/follow-up (FU) neuropsychological testing, missing or incomplete MR-imaging or with incident brain infarcts on FU-MRI were excluded. All assessments at baseline were carried out before the introduction of dopaminergic therapy. At the follow-up examination all patients were on dopaminergic treatment (supplemental.

2.3. Neuropsychological assessment

Two neuropsychologists (CT/FS-D and BM/JE) conducted a battery of neuropsychological tests [19] and interviews with the study participants at baseline (BL) and follow-up (FU). Movement Disorder Society criteria [19,24] were used to classify patients as having normal cognition (PD-Non-MCI), mild cognitive impairment (PD-MCI), or dementia (PD-D). Parkinson's disease dementia and MCI were classified according to criteria [19,24]. For the Level II classification of Parkinson's disease MCI we applied the criterion of a standard deviation of at least 1.5 in at least two of the following tests (impairment in either two tests in one cognitive domain or one impaired test in two different domains):

- Attention and working memory evaluated by the Trail Making Test

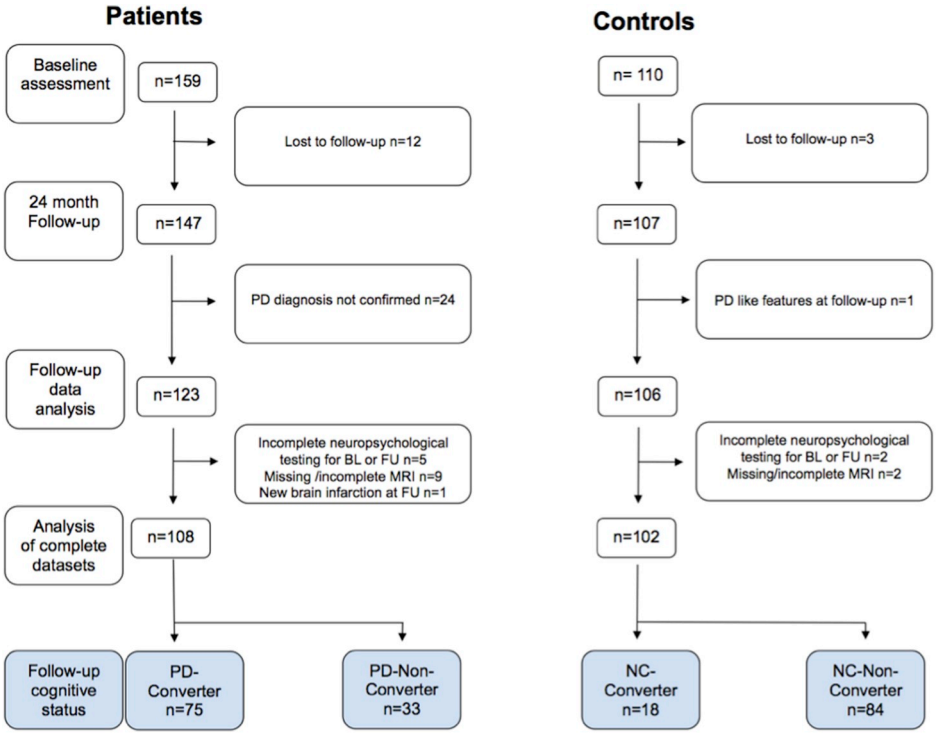

Fig. 1. Flowchart of enrolled and analyzed patients (PD) and healthy controls (NC) at baseline and follow-up with complete neuropsychological datasets with a final number of 108 patients and 102 healthy controls.
PD: Parkinson's Disease; NC: Non-PD control participant.

(TMT B/A) [25], digit span backward [21];
- Executive function tested by verbal fluency (animals) [26] and Stroop interference [27];
- Language was assessed by the similarity test [28] and the language subtest of MoCa [29];
- Memory was evaluated by verbal learning test [20] and forward digit span [21].
- Visuospatial function were delineated by cube analyses and fragmented letters [23].

The Mini Mental Status Examination (MMSE) [30] and Montreal Cognitive Assesment (MoCa) [31] were performed to evaluate the general cognitive status and the Beck's Depression Inventory (BDI) for presence and severity of depression.

2.4. Stratification of cognitive decline

For cross-sectional baseline comparisons the group of PD patients (PD) and the group of Non-PD controls (NC) were each divided into 2 groups according to their baseline cognitive status, resulting in the following four baseline groups: PD-MCI (MCI affected patients) and PD-N (patients with normal cognition); NC-MCI (MCI affected controls) and NC-N (controls with normal cognition).

Taking into account the longitudinal setting we also defined a group of “converters” for cognitive decline in the PD as well as in the control group that declined from normal cognition at BL to MCI/dementia at 24 month follow-up or from MCI to dementia at 24 month follow-up. Correspondingly, we defined a group of “non-converters”, who remained at their cognitive level (normal or MCI) or improved from MCI to normal cognitive status in the 24-month follow-up (Fig. 2) (see Fig. 3).

2.5. MR- imaging

All MRI images were acquired on 1.5 T systems (Philips Medical Systems, standard birdcage head coil). The protocol included an axial fluid-attenuated inversion recovery (FLAIR) sequence (TR): 6000 ms, echo time (TE) 120 ms) used for classification of WMHs. Additionally a transversal T2 (6 mm; TR 4800 ms; TE 110 ms); fast field echo T2 (T2*) (6 mm; TR 605 ms; TE 23 ms, flip angle 18°) as well as sagittal turbo far field T1 (1 mm; TR 7.5 ms; TE 3.5 mm, flip angle 8°). A total of 25 participants did not receive MRI due to contraindications (e.g. claustrophobia or pacemaker).

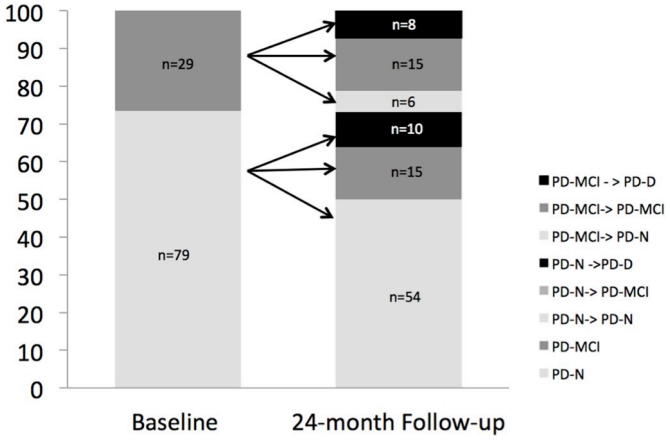

Fig. 2. Figure 2: Stratification of the 108 Parkinson's Disease Patients at baseline and 24-month follow-up based on the classification criteria for Parkinson's disease dementia (PD-D) and PD-MCI.
PD: Parkinson's Disease; NC: Non-PD control participant; MCI: Mild Cognitive Impairment; D: Dementia; PD-MCI: MCI affected patients and PD-N: patients with normal cognition.

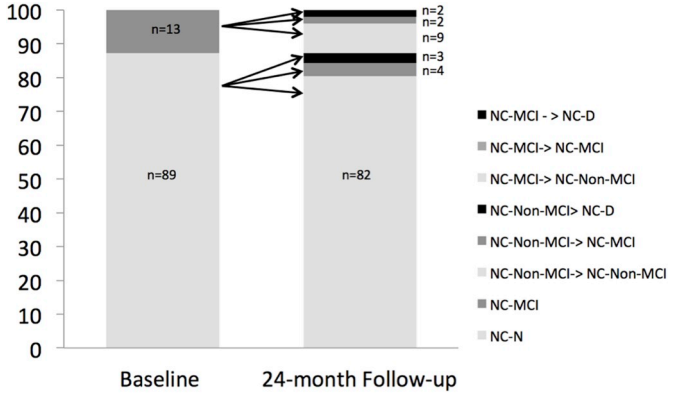

Fig. 3. Stratification of the 102 healthy controls at baseline and 24-month follow-up based on the classification criteria for Parkinson's disease dementia (PD-D) and PD-MCI.
PD: Parkinson's Disease; NC: Non-PD control participant; MCI: Mild Cognitive Impairment; D: Dementia; NC-MCI: MCI affected controls and NC-N: controls with normal cognition.

2.5.1. Brain volume

All T1-weighted images were segmented automatically using the freely available and established algorithm from the VBM8 toolbox (release r435) [http://dbm.neuro.uni-jena.de/vbm/] to obtain overall grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) volumes in millilitres and normalized to MNI (Montreal Neurological Institute) space in 1 mm cubic resolution. VBM8 is an extension of the Matlab (release R2012b) based software package SPM8 (Statistical Parametric Mapping) [http://www.fil.ion.ucl.ac.uk/spm/]. Afterwards, global tissue class volumes were estimated by summing up the all voxel probabilities per tissue class in native space (GM, WM, CSF). The total intracranial volume (TIV) was estimated by summing up all three volumes.

2.5.2. Generation of WMH-maps and -volume

All FLAIR images were semi-automatically segmented by an experienced neuroradiologist (auto-trace tool of ROI Editor in Analyze 11.0) to obtain binary white matter lesion maps. Afterwards the WMH volume was calculated.

2.5.3. Cholinergic Pathway Hyperintensities scale (CHIPS)

FLAIR images were used to evaluate WMHs in the cholinergic pathway applying the recently developed visual rating scale, CHIPS [12,13]. Precisely, WMH within the cholinergic pathways were visually rated on a three-point scale for 10 regions, using major anatomical landmarks (corona radiate, low and high external capsule and centrum semiovale) on four selected axial FLAIR images. All scans were assessed blinded to group assignment, clinical information and patients' cognitive status.

2.6. Statistical analysis

Univariable distribution of metric variables is described by median and interquartile range. For categorical data, absolute and relative frequencies are given. Mann–Whitney *U* test or χ [2] test was used to compare 2 independent samples on a metric or categorical outcome, respectively. The predictive roles of the global WMH volume and the CHIPS score regarding cognitive status were evaluated by separate multivariable logistic regression analyses adjusted for age, gender, and education. Due to the small volumes and skewed distribution of the global WMH load and the CHIPS score we used tertiles of these variables in the regression analyses (Table 1 and supp. 2). For all analyses two-tailed p-values were used, and $p < 0.05$ was regarded as significant. Statistical analyses were performed using the statistical

Table 1
Demographic, clinical and imaging characteristics at baseline of the 108 Parkinson's Disease patients stratified for cognitive status.

Baseline characteristics	PD-N (n = 79)	PD-MCI (n = 29)	p-value	PD-Non-Converter (n = 75)	PD-Converter (n = 33)	p-value
Demographics						
Age (years), mean (SD)	64 (9)	63 (10)	0.64	63 (10)	66 (8)	0.16
Women, n (%)	32 (41%)	9 (31%)	0.37	31 (41%)	10 (30%)	0.28
Years of schooling, median (IQR)	9.5 (8; 11)	8 (8; 10)	0.04	10 (8; 11)	9 (8; 10)	0.07
Motor scores						
UDPRS III, median (IQR)	14 (8; 22)	18 (14; 28)	0.01	14 (10; 22)	19 (11; 28)	0.13
Hoehn & Yahr, median (IQR)	1.5 (1; 2)	2 (1.3; 2.5)	0.06	1.5 (1; 2)	2 (1; 2.5)	0.10
Vascular risk factors						
Smoker (ever), n (%)	38 (48%)	14 (48%)	0.99	36 (48%)	16 (49%)	0.96
Hypertension*, n (%)	43 (54%)	19 (66%)	0.30	39 (52%)	23 (70%)	0.09
Diabetes mellitus*, n (%)	6 (8%)	2 (7%)	0.90	5 (7%)	3 (9%)	0.66
Hyperlipidamia, n (%)	32 (40.5%)	15 (51.7%)	0.30	35 (46.7%)	12 (36.4%)	0.32
Coronary heart disease, n (%)	6 (7.6%)	3 (10.3%)	0.65	6 (8%)	3 (9.1%)	0.85
Neuropsychiatric test scores						
MMSE, median (IQR)	29 (28; 30)	28 (28; 29)	0.001	29 (28; 30)	29 (28; 29)	0.16
MOCA, median (IQR)	26 (24; 28)	24 (22; 27)	0.02	26 (24; 28)	24 (22; 25)	< 0.001
FAI*, median (IQR)	55 (34; 89)	59 (31; 88)	0.94	53 (31; 89)	60 (39; 82)	0.62
GDS, median (IQR)	3 (1; 5)	3 (2; 6)	0.29	3 (1; 6)	3 (1; 5)	0.75
BDI**, median (IQR)	9 (4; 13)	7 (5; 16)	0.97	8 (3; 13)	8 (5; 14)	0.45
Imaging markers						
Absolute brain volume in ml, mean (SD)	1158 (111)	1190 (129)	0.20	1171 (115)	1156 (121)	0.53
Relative brain volume, mean (SD)	0.81 (0.03)	0.8 (0.02)	0.48	0.81 (0.03)	0.8 (0.02)	0.02
WMH (no lesions), n (%)	41 (52%)	12 (41%)	0.33	40 (53%)	13 (39%)	0.18
WMH, lesion volume < 1 ml, n (%)	24 (30%)	8 (28%)	0.32	20 (27%)	12 (36%)	0.40
WMH, lesion volume ≥ 1 ml, n (%)	14 (18%)	9 (31%)	0.31	15 (20%)	8 (24%)	0.42
WMH volume in ml, median (IQR)***	0.5 (0.1; 3.6)	1.0 (0.3; 2.9)	0.21	0.5 (0.2; 2.5)	0.5 (0.1; 3.8)	0.22
CHIPS, no lesion, n (%)	44 (56%)	16 (55%)	0.96	45 (60%)	15 (46%)	0.16
CHIPS score 1–6, n (%)	17 (22%)	5 (17%)	0.82	12 (16%)	10 (30%)	0.21
CHIPS score ≥7, n (%)	18 (23%)	8 (28%)	0.81	18 (24%)	8 (24%)	0.22
CHIPS Score, median (IQR)***	8 (3; 12)	12 (4; 21)	0.62	10 (3; 13)	6 (3; 14)	0.21

Abbreviations: PD: Parkinson's Disease; MCI: Mild Cognitive Impairment; UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MMSE: Mini Mental Status Examination, MOCA: Montreal Cognitive Assessment; FAI: Fatigue Assessment Inventory; BDI: Beck Depression Inventory Scale; MRI: magnetic resonance imaging; WMH: White Matter Hyperintensities; CHIPS: Cholinergic Pathway Hyperintensities Scale; SD: standard deviation; IQR: interquartile range (25th and 75th percentile); *self-report of physician diagnose; **missing data for BDI: 26 patients; *** estimated in the n = 55 subjects with WMH > 0, and the n = 48 subjects with CHIPS > 0, respectively.

software SPSS 25 (SPSS Inc., Chicago, IL).

3. Results

3.1. Study sample

Demographic and clinical baseline characteristics of the DeNoPa cohort (159 patients and 110 controls) have recently been published [15]. A total of 147 patients and 107 controls attended the follow-up visit. Parkinson diagnosis was clinically confirmed in 123 patients. The reassessment of clinical diagnosis revealed other neurological disorders in 24 (16%) of the patients after follow-up visit: Four were classified as suffering from progressive supranuclear palsy, four from multiple system atrophy (MSA-P), two from Dementia with Lewy Bodies, two from vascular parkinsonism, one from corticobasal degeneration, and in three cases the predominant movement abnormality was classified as essential tremor (n = 2) or as cerebellar tremor (n = 1). In 8 patients the final diagnosis remained unclear. One subject with MSA-P died after the 2FU visit, and autopsy confirmed the diagnosis of MSA-P. One healthy control developed an irregular resting tremor in one arm between assessments and was therefore excluded from further analysis [16]. Five patients with missing or incomplete neurophysiological testing (n = 5), missing or incomplete MR-imaging (n = 9) or with incident brain infarcts on MRI (n = 1) were excluded for the current analysis leaving a total of 108 Parkinson's disease patients with complete data at baseline and 24-month follow-up. In the control group (n = 107) four subjects were excluded due to missing/incomplete baseline imaging or neuropsychological testing leaving 102 control participants for analysis (Fig. 1).

3.2. Cognitive status at baseline with comparison of baseline characteristics

A total of 29 (26.9%) PD patients met the criteria for MCI at baseline (PD-MCI); the remaining 79 (73%) patients were cognitively normal, i.e. they did not fulfil the criteria for MCI or dementia (PD-N). Clinical variables, imaging markers and cognitive scores for Parkinson's disease patients stratified for cognitive status at baseline are illustrated in Table 1 (left panels). PD-MCI patients showed a lower proportion of women, a slightly lower level of education, and more severe motor symptoms compared to cognitively normal PD patients. There were no remarkable differences in age or vascular risk factors with the exception of arterial hypertension, which was more frequent in PD-MCI patients (Table 1, left panels). As expected, general cognitive abilities evaluated by the MOCA- and MMSE-score were lower in patients with PD-MCI than in PD-N patients. Regarding imaging markers, PD-MCI compared to PD-N patients more often presented with WMH (59% vs. 48%), particularly with large lesion volumes > 1 ml (31% vs. 18%) and high CHIPS scores (28% vs. 23% for the highest CHIPS score tertile).

For the 102 participants in the control group (suppl. Table 2, left panels) participants with mild cognitive impairment (NC-MCI) also showed fewer women and slightly lower education levels than cognitively normal participants (NC–N). All vascular risk factors were more frequent in cognitively impaired participants. By design, the MOCA score was lower in the NC-MCI group compared to the NC-N group. As in PD patients, controls with MCI more often presented with large WMH volumes > 1 ml (31% vs. 18%) and high CHIPS scores (46% vs. 23% for the highest CHIPS score tertile) compare to the cognitively unimpaired controls.

Table 2
Multivariable logistic regression analyses on cognitive status at baseline in Parkinson's Disease patients (n = 108).

	Global WMH volume		CHIPS score	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Age, per year increase	0.95 (0.89–1.01)	0.08	0.96 (0.90–1.01)	0.15
Women	0.60 (0.23–1.57)	0.30	0.61 (0.24–1.57)	0.31
Education, per school year increase	0.58 (0.39–0.87)	0.58	0.60 (0.41–0.89)	0.01
WMH, no lesions (reference)	–		–	
WMH, lesion volume < 1 ml	1.06 (0.36–3.11)	0.91	–	
WMH, lesion volume ≥ 1 ml	2.92 (0.90–9.42)	0.07	–	
CHIPS, no lesions (reference)	–		–	
CHIPS score 1–6	–		0.75 (0.23–2.46)	0.64
CHIPS score ≥7	–		1.33 (0.45–3.95)	0.64

Abbreviations: WMH: White Matter Hyperintensities; CHIPS: Cholinergic Pathway Hyperintensities Scale; OR: Odds Ratio; CI: confidence interval.

3.3. Cognitive course over 24-month with comparison of baseline characteristics

After a follow up period of on average 24-month 33 (30.6%) PD patients cognitively declined whereas 75 (69.4%) PD patients remained cognitively stable. More precisely, in the "converter group" 10 (30.3%) PD patients directly declined from cognitive normal status to dementia, 15 (45.5%) patients declined from normal cognition to mild cognitive impairment and 8 (24.2%) patients progressed from MCI to dementia. In the PD Non-Converter group 54 (72%) patients remained stable at a cognitively normal level and 15 (20%) patients at MCI level; an additional 6 (8%) patients improved from MCI status to normal cognitive status (Fig. 2). Patients in the PD converter group were at baseline older than patients in the PD non-converter group (Table 1, right panels). They were also more often men, had a slightly lower level of education and were often diagnosed with hypertension. Regarding imaging markers, global WMH were more frequent in PD converters (61% vs. 47%), mainly driven by patients with small WMH volumes. However, cholinergic WMH load at baseline was not higher in PD converters compared to PD non-converters.

In the non-PD control group a higher proportion of men, slightly lower education levels, and a higher prevalence of cardiovascular risk factors were observed in converters compared to non-converters (suppl. Table 2, right panels). Regarding imaging markers, there were no remarkable differences in the presence or load of global or cholinergic white matter lesions.

3.4. Association of imaging markers with cognitive status at baseline

Multivariable logistic regression analyses adjusted for age, gender, education and relative brain parenchyma volume revealed no association between global WMH presence and cognitive status at baseline in PD patients (Table 2). There was, however, a nearly three-times higher odds of being an MCI patient for the highest compared to the lowest tertile (no lesions) of WMH also no association between the presence of cholinergic lesions (OR 1.01; 95% CI 0.41–2.51) or the semi-quantitative CHIPS score (OR 1.16; 95% CI 0.79–1.72) with cognitive status in PD patients at baseline (Table 2). Similarly, in participants of the control group neither WMH presence (OR 0.85; 95% CI 0.24–2.98), or volume (OR 1.72; 95% CI 0.91–3.38), nor the presence of cholinergic lesions (OR 1.18; 95% CI 0.33–4.19) or the CHIPS score (OR 1.42; 95% CI 0.80–2.50) were associated with cognitive status at baseline (suppl. Table 3).

3.5. Association of imaging markers with cognitive decline

Multivariable logistic regression analyses adjusted for age, gender, education and relative brain parenchyma volume revealed no association between global WMH presence (OR 1.54; 95% CI 0.64–3.68) or volume (OR 1.42; 95% CI 0.84–2.41) with cognitive decline in PD patients during the 24-month follow-up (Table 3). There was also no association between the presence of cholinergic lesions (OR 1.62; 95% CI 0.68–3.86) or the semiquantitative CHIPS score (OR 1.19; 95% CI 0.82–1.71) with cognitive decline in PD patients during the 24-month follow-up (Table 3).

Similarly, in participants of the control group neither WMH presence (OR 0.92; 95% CI 0.31–2.72) or WMH volume (OR 1.38; 95% CI 0.76–2.50), nor the presence of cholinergic lesions (OR 1.33; 95% CI 0.45–3.93) or the CHIPS score (OR 1.32; 95% CI 0.81–2.16) were associated with cognitive decline over 24 months (suppl. Table 4).

4. Discussion

In our longitudinal single-centre DeNoPa cohort we found no evidence that WMH, measured as global lesion volume and as strategic lesion load within cholinergic pathways, are associated with cross-sectional cognitive impairment or longitudinal cognitive decline in early PD patients.

The results of the present study are in line with some previous imaging studies suggesting that macroscopic white matter hyperintensities are not a sensitive predictor of cognitive decline in early Parkinson's disease [8,9,11]. A cross-sectional study of Dalaker et al., for example, compared newly diagnosed PD patients with MCI, PD patients without MCI and normal controls [11]. MCI was classified based on performance in three different cognitive domains and according to a modified version of the criteria for MCI [32]. The study revealed no significant differences between total WMH volume in PD patients and normal controls, independent whether PD patients were presenting with MCI or not [11]. Similar to our study, Dalakar et al. used a case control design and recruited newly diagnosed treatment naive patients. Our results corroborate their finding and extend it to a longitudinal setting as well as to a more specific WMH measure.

Gonzalez-Redondo et al. [9] performed a cross-sectional study with 111 PD patients and a longitudinal study with 36 PD patients from the same cohort. Patients were classified as showing normal cognition, mild cognitive impairment, or dementia. The cross-sectional revealed no significant differences in the WMH volume among the groups. The authors observed a mild association of the increase WMHs (periventricular and total burden) with progression of cognitive decline. In contrast to our study they used a visual rating scale to determine global WMH load [33]. Furthermore, the follow-up cohort was small so that these results should be interpreted with caution.

Recently, Malek et al. [10] conducted a cross-sectional study with 1756 PD patients with PD diagnosis in the preceding 3.5 years. They reported that cognitive impairment was more prevalent in those PD patients with multiple vascular risk factors. In contrast to our study, also patients with history of stroke were included. Their definition of the presence of MCI only based on the MoCa, but not on the more precise Movement Disorder Society criteria [19,24], taking into account more cognitive domains (executive function, attention and speech [25],

Table 3
Multivariable logistic regression analyses on the risk of becoming a 'cognitive converter' in Parkinson's Disease patients (n = 108).

	Global WMH volume	p-value	CHIPS score	p-value
	OR (95%CI)		OR (95%CI)	
Age, per year increase	1.02 (0.97–1.08)	0.43	1.02 (0.97–1.08)	0.39
Women	0.59 (0.24–1.47)	0.26	0.57 (0.23–1.41)	0.22
Education, per school year increase	0.76 (0.56–1.03)	0.07	0.76 (0.56–1.03)	0.08
WMH, no lesions (reference)	–		–	
WMH, lesion volume < 1 ml	1.64 (0.62–4.37)	0.32	–	
WMH, lesion volume ≥ 1 ml	1.43 (0.46–4.41)	0.53	–	
CHIPS, no lesions (reference)	–		–	
CHIPS score 1–6	–		2.29 (0.80–6.58)	0.12
CHIPS score ≥7	–		1.13 (0.39–3.29)	0.82

Four different regression models showing no association between global WMH presence or volume and the semiquantitative CHIPS score with cognitive decline in PD patients during the 24-month follow-up.
WMH: White Matter Hyperintensities; CHIPS: Cholinergic Pathway Hyperintensities Scale; OR: Odds Ratio; CI: confidence interval.

memory [20–22] and visuospatial function [15,23]). Therefore, the different ascertainment of cognitive status might be a potential reason for the different results. Compta et al. [7] observed in their cross-sectional study a greater proportion of cases with moderate-to-severe parieto-occipital WMHs compared to the non-demented PD patients and controls.

Besides semi-automated assessment of WMH, we additionally classified WMH located on cholinergic fibers by using the CHIPS score However, this score revealed no relevant impact on cognitive decline in our study sample. This is in contrast to recent cross- and longitudinal Korean studies [13,14]. However, both Korean studies used the Seoul neuropsychological screening battery [34] for the assessment of cognitive decline, whereas we used a specific battery of neuropsychological tests designed to measure cognition specifically in PD patients [24]. Furthermore, PD patients in the Korean cohorts were included in a more advanced stage of Parkinson's disease, as shown by higher UDPRS-III scales of the included PD patients [13].

PD patients and normal controls showed approximately the same effect sizes concerning WMH and the CHIPS score. Consequently, WMH might have the same contributing factor in PD patients and controls. Although WMH are a common surrogate marker and known to predict cognitive decline in the elderly [5], there was no relevant impact of WMH on cognition or cognitive decline in the controls of our study. One reason might be the relatively small sample size and the relatively short follow-up period of 24 months.

Some limitations in our study need to be addressed. The initial cognitive test battery was analysed in drug-naïve patients whereas all PD patients received a dopaminergic medication during follow-up. This might result in an underestimation of cognitive decline and might be an explanation why some patients showed an improvement in cognitive performance after 24 month. The DeNoPa cohort is a longitudinal study with a planned follow up period of 10 years. Therefore a re-evaluation of the impact of WMH on cognitive conversion rates in the long term is possible. The contributing role of WMH on cognitive decline might be apparent in the later course of the PD disease [35]. As the presence of dementia significantly decreases quality of life and increases caregiver burden, there is a need to further investigate the underlying mechanisms of cognitive decline in PD and to identify potential markers that may predict cognitive decline in order to develop targeted therapeutic and preventive strategies.

5. Conclusions

WMH as marker of subclinical vascular brain disease were not associated with cognitive function or decline in our cohort of de novo PD patients and controls.

Authors' roles

1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique

U. H.: 1A-C, 2A-B, 3A
A. T.: 1B–C, 2C, 3B
M. S.: 1C, 3B
E. L..: 1C, 3B
C. T.: 1B–C, 3B
B. M.: 1A-B, 2C, 3B
H. M.: 1A, 2A, 2C, 3B

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.10.016.

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