I.R.C.C.S. Ospedale San Raffaele

LONGITUDINAL EVOLUTION OF WHITE MATTER DAMAGE IN PARKINSON'S DISEASE

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BACKGROUND

- White matter hyperintensities (WMH) increase in frequency and volume with age (de Leeuw et al., 2001) and are associated with cognitive decline in normal aging (Garde et al., 2000).

- In Parkinson's Disease (PD) the relationship between cognitive disfunction and WMHs is controversial:
  - Significant association between WMH and cognitive and motor impairment based on cross sectional data (Shin et al. 2012; Kandiah et al. 2013; Pozorski et al. 2019).
  - Baseline WMH was associated cross-sectionally and longitudinally with the prevalence of dementia but these relationships became statistically insignificant after adjusting for age and education (Lee et al. 2016).
  - Other longitudinal studies showed no association between cognitive change and WMH progression (Sunwoo et al. 2014; Pozorski et al. 2019).

BACKGROUND

- **Many studies showed WM microstructural damage related metrics alteration (i.e. fractional anisotropy decrease and mean diffusivity increase) in several regions and correlation between diffusion tensor imaging (DTI) metrics and cognitive and motor assessment (Atkinson-Clement et al., 2016).**

- **Only a few studies focused on longitudinal characterization of DTI alterations in PD:**
  - **Some studies showed significant diffuse FA decrease and MD increase, with no significant association with cognitive and motor impairment (Minett et al., 2018; Pozorski et al., 2018),**
  - **Another one showed significant association with clinical data (Taylor et al., 2018).**

AIM OF THE STUDY

The aim of our study was to investigate the longitudinal evolution of cerebral white matter micro- and macrostructural damage and its relationship with motor and non-motor symptoms in PD

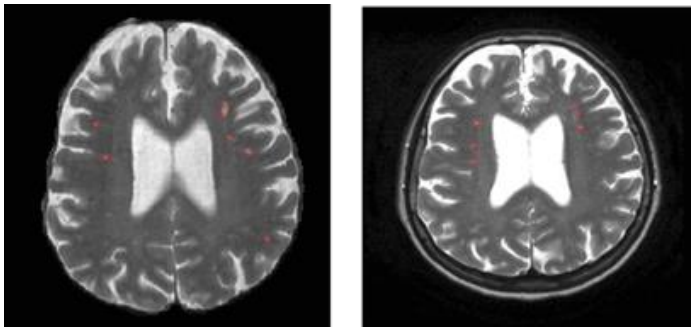
MATERIALS AND METHODS

Subjects. 154 patients with PD underwent clinical assessment, cognitive evaluation and MRI scan on a 1.5 Tesla scanner (including T2-weighted and diffusion tensor [DT] MRI sequences) once a year over a follow-up time of 36 months.

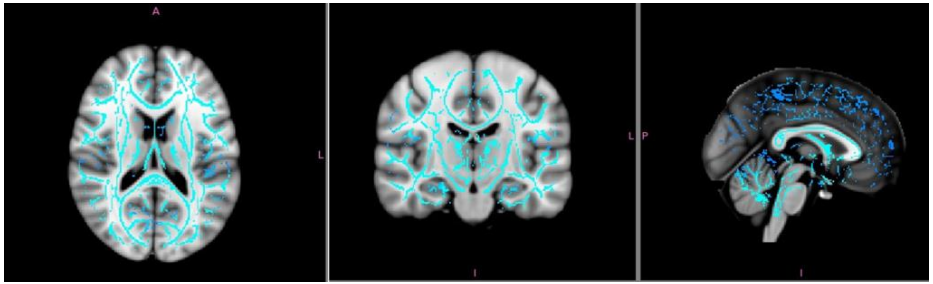
Variable	
Gender (M/F)	91/63
Age (mean)	61.6 ± 7.9 (39.4 - 83)
Age at onset (mean)	56.6 ± 8.3 (38 - 71)
PD duration (mean)	4.9 ± 4.8 (0 - 23.9)
H&Y (mean)	1.7 ± 0.8 (1 - 4)
Education (mean years)	12.5 ± 2.6 (4 - 20)
Family history (yes/no)	24/130
Asymmetry (yes/no)	148/6
Side onset (right/left/symmetric)	97/54/3
Handedness (right/left/ambi)	144/6/1

MATERIALS AND METHODS

MRI analysis. White matter lesions (WML) were manually identified on T2-weighted scans and the total WML volume was calculated for each subject.



Applying tract-based spatial statistics (TBSS), mean fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (axD) and radial diffusivity (radD) values of the total WM skeleton were extracted.



Statistical analysis. Longitudinal regression models, adjusting for baseline motor impairment measured using the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) and Pearson correlation analyses between MRI and clinical/cognitive data were performed.

RESULTS – Baseline – Correlation analysis

Variable 1	Variable 2	Correlation (r)	p-value
WML	FA	-0.18	**0.03**
	MD	0.17	**0.04**
	axD	0.11	0.17
	radD	0.18	**0.03**
	UPDRSIII	0.17	**0.04**
	MMSE	-0.23	**0.05**
	ACEtot	-0.20	**0.01**
FA	UPDRSIII	-0.21	**0.01**
	MMSE	0.27	**0.01**
	ACEtot	0.17	0.49

Variable 1	Variable 2	Correlation (r)	p-value
MD	UPDRSIII	0.23	**0.01**
	MMSE	-0.26	**0.01**
	ACEtot	-0.07	0.39
axD	UPDRSIII	0.13	0.10
	MMSE	-0.17	**0.04**
	ACEtot	-0.04	0.63
radD	UPDRSIII	0.25	**0.02**
	MMSE	-0.29	**<0.001**
	ACEtot	-0.12	0.15

ACE: Addensbrooke's Cognitive Examination; **axD**: axial diffusivity; **FA**: fractional anisotropy; **MD**: mean diffusivity; **MMSE**: Mini Mental State Examination; **radD**: radial diffusivity; **UPDRS**: Unified Parkinson's Disease Rating Scale; **WML**: white matter lesions.

RESULTS – Longitudinal Regression Analysis

UPDRS-III score, WML volume and MMSE showed significant progression over follow-up.

Clinical/cognitive variables	Slope	SE	p-value
UPDRS III	3.8933	0.2656	**<0.0001**
MMSE	-0.2557	0.0558	**<0.0001**
ACEtot	-0.3647	0.2076	0.08
MRI variables	**Slope**	**SE**	**p-value**
WML	0.1945	0.0096	**<0.0001**
FA	-0.0003	0.0003	0.22
MD	-0.0026	0.0017	0.12
axD	-0.0046	0.0025	0.06
radD	-0.0015	0.0013	0.25

ACE: Addensbrooke's Cognitive Examination; **axD**: axial diffusivity; **FA**: fractional anisotropy; **MD**: mean diffusivity; **MMSE**: Mini Mental State Examination; **radD**: radial diffusivity; **UPDRS**: Unified Parkinson's Disease Rating Scale; **WML**: white matter lesions.

RESULTS – Longitudinal – Correlation analysis

Variable 1	Variable 2	Correlation (r)	p-value
UPDRSIII	MMSE	-0.01	0.96
	ACEtot	-0.03	0.82
	WML	-0.04	0.78
	FA	-0.14	0.26
	MD	0.30	**0.01**
	axD	0.37	**0.0016**
	radD	0.24	**0.05**
MMSE	ACEtot	0.62	**<0.0001**
	WML	-0.05	0.68
	FA	0.08	0.54
	MD	-0.13	0.31
	axD	-0.15	0.24
	radD	-0.11	0.38
ACEtot	WML	-0.03	0.81
	FA	0.24	0.06
	MD	-0.29	**0.02**
	axD	-0.27	**0.02**
	radD	-0.27	**0.02**
WML	FA	-0.07	0.60
	MD	-0.10	0.43
	axD	-0.20	0.11
	radD	-0.04	0.78

Longitudinal trajectories of MD, axD, and radD values significantly correlated with UPDRS-III and ACE total score.

WML volume did not correlate with longitudinal alterations of motor and cognitive clinical variables.

ACE: Addensbrooke's Cognitive Examination; **axD**: axial diffusivity; **FA**: fractional anisotropy; **LED**: L-dopa equivalent dose; **MD**: mean diffusivity; **MMSE**: Mini Mental State Examination; **radD**: radial diffusivity; **UPDRS**: Unified Parkinson's Disease Rating Scale; **WML**: white matter lesions.

DISCUSSION and CONCLUSIONS

- **WML, FA and MD at baseline is associated with cognitive and motor status**
- **Longitudinal evolution of WM microstructural damage is associated with both motor and cognitive deterioration.**
- **Increase over time of WM macroscopic alterations is not associated with motor and cognitive deterioration.**
- **Our results suggest that longitudinal evolution of WM microstructural damage measured by DT MRI might provide a sensitive biomarker of disease progression in PD.**