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Research Article

Differential Impact of Periventricular and Deep White Matter Lesions in Parkinson's Disease

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Abstract

Background: The clinical significance of white matter lesions (WML) is still controversial in PD. Studies differ in the differentiation between periventricular (PWML) and deep white matter lesions (DWML), the use of automated versus semi-quantitative methods to measure those and the measurement of lesion volume. Our goal was to study the burden of WML in motor and non-motor symptoms of PD, addressing those above-mentioned shortcomings.

Methods: We evaluated 77 patients with PD using a standardized clinical and imaging protocol. We used FLAIR images sequence and ITK-SNAP software for segmentation into DWML and PWML, which calculate the volume of the lesions automatically. We used generalized linear model to analyze the relationship between WML and clinical characteristics as evaluated by clinical scales ($p < 0.05$).

Results: In the univariate analysis, higher volume of DWML ($p = 0.007$), PWML ($p < 0.001$) and total WML ($p = 0.001$), was associated with higher UPDRS-III score. Conversely, lower SCOPA-COG were associated with higher PWML ($p = 0.018$) and total WML ($p = 0.030$) volume. In the multivariate analysis, higher volume of PWML ($p = 0.01$) was associated to higher UPDRS-III score. There was no association between WML volume, neither DWML, nor PWML, with non-motor symptoms as assessed by the non-motor symptom scale (NMSS).

Conclusion: We observed an association between the volume of the WML, mostly periventricular, and the severity of cognitive and motors symptoms, adjusting for clinical characteristics known to influence disease progression.

Keywords: *Parkinson's Disease; Periventricular White Matter Lesion, Deep White Matter Lesion*

Introduction

Parkinson's disease (PD) is characterized by degeneration of the substantia nigra pars compacta dopaminergic neurons with resultant widespread loss of dopaminergic innervation. However, it is clear that more widespread degeneration occurs in the disease [1] and the current knowledge on its pathophysiology is not sufficient for understanding its clinical heterogeneity.

White matter lesions have been described in a variety of neurologic and systemic diseases as well as in healthy subjects [2]. White matter lesions (WML) or white matter hyperintensities (WMH) are abnormalities commonly found in the elderly in T2-weighted se-

quences and fluid attenuated inversion recovery (FLAIR). Even though it is known that the prevalence increases with age [3], the clinical significance of WML is still controversial. WML are classified into two different subtypes: periventricular (PWML) and deep (DWML) [4]. Irregular PWMLs are likely secondary to chronic hemodynamic insufficiency, whereas DWMLs are probably determined by small vessel disease [5]. Clinically, PWML are usually associated to cognitive decline, while DWML are associated with mood disorders [2], gait changes and urinary incontinence [6].

The burden of WML differs between individuals with PD and age matched controls [7]. The presence of WML seems to have a role in axial motor impairment and possibly cognitive decline in PD [8]. However, there was marked variability and inconsistency between study results: most studies did not differentiate between PWML and DWML, use of 1.5 versus 3T magnets, white matter lesion quantification by automated or semi-quantitative methods, and the definition of the lesion based on volume [8].

Objective of the Study

Thus, our objective was to study the relationship between volume of PWML and DWML in motor and non-motor symptoms of PD, controlling for possible confounding factors such as age, sex and disease duration.

Methods

Participants

The Ethics Committee of the University Hospital-UNICAMP approved the study. Between February 2011 and June 2013 three experienced Movement Disorders Specialist assessed all patients. All individuals were recruited at the Movement Disorders Clinic at the University Hospital-UNICAMP and signed an informed consent prior to any research related procedure.

A total of 77 patients with PD diagnosed according to the UK Parkinson's Disease Society Brain Bank criteria were recruited for this study (Table 1) [9]. Evaluation consisted of a standard questionnaire, which included information on sex, age, age at onset, PD medical history, side of onset of the symptoms, family history, professional history and medication used, as well as physical and neurological examination and application of the following scales: Unified Parkinson's Disease Rating Scale (UPDRS), Modified Hoehn and Yahr staging (HY) [10], Scales for Outcomes of Parkinson's disease - Cognitive (SCOPA-COG) [11], Non-motor symptom scale (NMSS) [12] and Schwab and England Activities of Daily Living [13].

Male n (%)	51 (71.83)
Age (y)*	58.70 (10.05)
Mean disease duration (y)	8.36 (6.98)
Side of onset - right n (%)	31 (43.66)
UPDRS-III*	15.83 (8.18)
SCOPA-COG*	20.06 (6.13)
NMSS*	66.96 (44.75)
SCHWAB*	0.74 (0.21)
H&Y*	2.47 (6.13)

Table 1*: Demographics.*
*n: Number of Subjects; y: Years; * = Mean Score (SD); SD: Standard Deviation.*

Image acquisition and analysis

All subjects underwent MRI imaging on a 3 Tesla Philips Achieva System. We acquired high-resolution volumetric T1- weighted sequence (axial acquisition, TR 7.1 ms, TE 3.3 ms, TI 850 ms, FOV 240 x 240 mm^2, matrix 256 x 256, slice thickness 1 mm, total 210 slices, scan time 6'), volumetric T2- weighted sequence (axial acquisition, TR 7,1 ms, TE 3.3 ms, TI 850 ms, FOV 240 x 240 mm^2, matrix 448 x 448, slice thickness 3 mm, total 70 images, scan time 3') and whole brain fluid attenuated inversion recovery (FLAIR) images, (axial acquisition, with isotropic voxels of 0.9 mm; TR 12000 ms; TE 140 ms; T1 2850 ms; FOV 240 x 240 mm^2; matrix 224 x 160; slice thickness 4 mm; total 30 slices, scan time 3').

An experienced neuroradiologist carefully analyzed all images in a blinded fashion, masked for patient diagnosis, to guarantee the absence of movement artifacts and pathological abnormalities. Six subjects were excluded due to motion artifact, resulting in a final sample of 71 participants (Table 1). We used the FLAIR sequence, on DICOM format to manually segment WML on ITK-SNAP [14,15]. Segmentation of PWML and DWML were made separately, by visual criteria, without any prior access to patient´s data. WMLs more than 10 mm from the ventricular surface were classified as DWML, those between 0 and 10 mm of ventricular surface as PVWML. For each subject at a time, segmentation started by uploading the FLAIR sequence images to the program and by auto adjusting its contrast. First, lesions were simply marked on a grayscale (Figure 1) with zoom adjusted to 2.5 pixels/mm^2, slice by slice in cranio-caudal order. We then returned in the opposite direction on a hot scale (Figure 1), continuing to simply mark lesions. We used the coronal view at this point to check the segmentation. An experienced neuroradiologist reviewed this process following the same steps. Going back to the axial grayscale, images were then zoomed to 5 pixels/mm^2 and all marked lesions were segmented. After segmenting both PWML and DWML, we simultaneous displayed both segmentations to ensure that there was no overlap between them. The software automatically calculated the volume of the lesions.

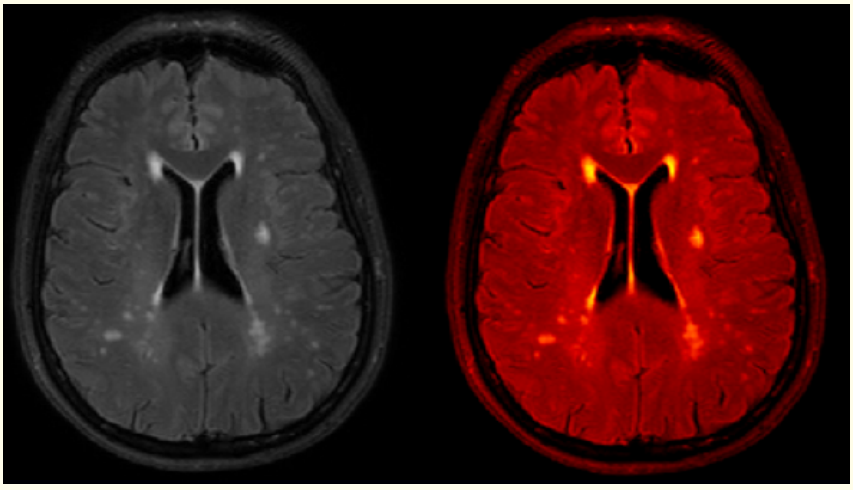

Figure 1: *Standard image scale for segmentation. Images on grayscale (left) and hotscale (right).*

Statistical analysis

For the statistical analysis we used STATA 13.1 version. Level of significance was set at $p < 0.05$. We performed generalized linear models (GLM - family Gaussian, link identity). The dependent variable was each clinical score (UPDRS subscale 3 (UPDRS-III), SCOPA-COG and

NMSS). At first, we performed a univariate analysis using volume of PWML, volume DWML and total volume of WML as the independent variables. Later, we included both the volume of PWML and of DWML in the same model as independent variables. All analyses were adjusted for sex, age, and disease duration. For the models with SCOPA as the dependent variable we also controlled for years of education.

Results

Sixty-nine PD patients presented WMLs (97.18%), from which 62 had PWML (87.32%) and 60 DWML (84.51%). Mean total volume of WML was 1841.62 ± 4733.98 pixels, mean volume of PWML was 841.32 ± 2159.31 pixels and for DWML was 1000.30 ± 2786.27 pixels.

In the univariate analysis, for every increase of 0.008 pixels in the volume of DWML (p = 0.007), 0.0015 pixels in PWML volume (p < 0.001) and 0.0006 pixels in total WML (p = 0.001), there would be an increase in one point in UPDRS-III score. Conversely, for the SCOPA-COG, for every increase of 0.0007 pixels in PWML (p = 0.018) and 0.0003 in WML (p = 0.030) there would be a one-point decrease in the score. In the multivariate analysis, for every increase of 0.002 pixels in the volume of PWML (p = 0.01), there would be an increase in one point in UPDRS-III score.

There was no association between WML volume, neither DWML, nor PWML, with non-motor symptoms as assessed by the non-motor symptom scale (NMSS).

Univariate analysis controlling for sex, age, disease duration, and years of education (model including SCOPA)					
UPDRS-III	**Coef.**	**SE**	**z**	**p**	**95%CI**
DWML	0.0008	0.0003	2.70	0.007	0.0002 0.0014
PWML	0.0015	0.0004	3.74	0.000	0.0007 0.0023
WML (total)	0.0006	0.0002	3.24	0.001	0.0002 0.0009
SCOPA-COG	**Coef.**	**SE**	**z**	**p**	**95%IC**
DWML	-0.0004	0.0002	-1.90	0.057	-0.0008 0.00001
PWML	-0.0007	0.0003	-2.38	0.018	-0.0013 -0.0001
WML (total)	-0.0003	0.0001	-2.17	0.030	-0.0005 -0.00002
NMSS	**Coef.**	**SE**	**z**	**p**	**95%IC**
DWML	0.0009	0.0017	0.55	0.585	-0.0025 0.0044
PWML	0.0027	0.0025	1.07	0.286	-0.0023 0.0078
WML (total)	0.0008	0.0010	0.78	0.433	-0.0012 0.0029
Multivariate analysis controlling for sex, age, disease duration, and years of education (model including SCOPA only)					
UPDRS-III	**Coef.**	**SE**	**z**	**p**	**95%CI**
DWML	-0.0004	0.0005	-0.77	0.439	-0.0015 0.0006
PWML	0.0020	0.0008	2.56	0.010	0.0005 0.0036
SCOPA-COG	**Coef.**	**SE**	**z**	**p**	**95%IC**
DWML	0.0001	0.0004	0.21	0.837	-0.0007 0.0009
PWML	-0.0008	0.0006	-1.39	0.165	-0.0019 0.0003
NMSS	**Coef.**	**SE**	**z**	**p**	**95%IC**
DWML	-0.0025	0.0034	-0.72	0.469	-0.0094 0.0043
PWML	0.0059	0.0050	1.16	0.245	-0.0040 0.0159

Table 2: *Univariate analysis and multivariate analysis controlled for sex, age, disease duration and years of schooling (SCOPA-COG only).*

Coef.: Coefficient; SE: Standard Error; z: z Score; p: p-Value; CI: Confidence Interval.

Discussion

In order to perform a detailed and objective analysis, we classified WMLs volume into PWML and DWML, a differentiation not systematically done in previous studies [16-18]. We demonstrated a relationship between total volume of WML and the severity of motor and cognitive symptoms in PD. PWLM seems to independently contribute to deterioration in motor function.

WML accumulation is associated with aging [19]. WML may modify brain function by altering brain plasticity and decreasing functional reserve, leading to numerous clinical syndromes, yet there is great inter-individual variability [20]. WMLs in the frontal lobe and in the periventricular regions in non-PD patients strongly correlate with balance disorders, gait and mobility, yet falls is only observed in those with high WMLs volume [21]. Confluent DWMLs in non-PD patients are linked to cognitive decline, cerebrovascular disease and functional decline [20].

We observed a positive relationship between the volume of WMLs and the severity of motor symptoms measured by the UPDRS-III. We did not address which symptoms contributed most to this association. However, in our sample the correlation between the scores of the UPDRS-III and H&Y was high (σ = 0.73 0.76, p = 0.0000; results not shown). H&Y scores are directly related to postural changes and balance. In PD, evidence suggests that the presence of WML contributes independently to axial symptoms, particularly rigidity and bradykinesia, leading to lower scores on tests of gait and balance [22] and faster disease progression [23]. Patients with freezing present microstructural changes in white matter tracts that project to frontal areas associated to motor, sensory and cognitive functions [24]. Vascular lesions may contribute to the onset or worsening of freezing in PD patients [25].

Cognitive decline is associated with the presence of WML. PWML has significant negative impact on cognitive abilities of the elderly in the general population and the same was observed in our study [26]. Clinical presentation of cognitive dysfunction is heterogeneous due to the complexity of the interaction between cognitive reserve, brain volume, presence of comorbidities, family history and apolipoprotein E (APOE) status [19,20,27,28]. Nonetheless, WML burden contributes to dementia in the absence of concomitant Alzheimer's disease pathology, hippocampal sclerosis, vascular dementia or progressive supranuclear palsy [29]. The presence of WML also contributes to the progression of cognitive dysfunction in PD [29]. We did not observe an association between SCOPA-COG scores and DWML, contrary to findings suggesting the association between DWML and olfactory dysfunction. The discrepancy is probably due to the methodology used to quantify the lesions (quantitative versus semi-quantitative) and the differences between cognitive assessment.

We found no association between NMSS scores and WMLs. Although we considered it surprising, the NMSS is a scale that encompasses multiple different domains, which may have led to a very large variability in scores, hence decreasing the power of the analysis.

These findings raise the question of whether a more aggressive control of risk factors for WML would alter disease progression in PD. At this moment, there is no evidence to substantiate that. Targets for primary and secondary prevention of WMLs are hypertension, obesity, diabetes, hypercholesterolaemia and smoking [30-34]. Lifestyle interventions reduced the impact of diabetes in brain structure. They do not seem to influence cognitive outcomes though [33]. Blood pressure control appears to be an important factor in younger subjects with fewer WMLs at baseline, but not in older subjects or those with a high lesion volume. Cholesterol levels and the use of statins are also controversial [35].

Limitation of the Study

The two main limitations of our study are the relatively small sample size and the lack of complete information on risk factors. Unfortunately, despite the prospective nature of the study, many subjects were not able to provide full information about risk factors, and we did not have access to their detailed medical histories. We therefore did not believe this data was sufficiently reliable to be included in the study analysis. In addition, we evaluated the presence of symptoms as measured by clinical scales. Future studies should require associ-

ated diagnoses, such as depression or bladder dysfunction to be made on strict clinical criteria, not by history alone. Finally, our study is transversal and not longitudinal. A longitudinal study considering the presence of risk factors and adequate control of those would lead to a better understanding of how WMLs influence the symptoms and its treatment or how preventive measures are likely to have a modifying effect on disease progression. Conversely, the strong points are the use of a quantitative method rather than a qualitative one and the differentiation between DWML and PWML, showing that both are important and correlated with PD symptoms, even though they have different physiopathology. Lastly, we addressed motor and non-motor symptom concomitantly in the same patient population.

Conclusion

In summary, the presence of WML contributes for the severity of motor and non-motor symptoms, adjusting for clinical features known to influence disease progression. PWMLs seem to have a stronger effect than DWML. These observations need to be taken into account when interpreting PD symptoms, disease progression and responses to medication trials.

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Competing Interests Statements

None of the authors have conflicts of interest directly related to the development of the manuscript.

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Contributorship Statement

1) Research project:

   A. Conception: Juliana R Zuiani, Anelyssa D'Abreu; Joseph H Friedman, Fernando Cendes.

   B. Organization: Juliana R Zuiani, Anelyssa D'Abreu; Luiza G Piovesana; Lidiane S Campos; Rachel P Guimarães; Paula Azevedo; Fernando Cendes.

C. Execution: Juliana R Zuiani, Maria C A Santos; Camila C Piccinin; Luiza G Piovesana; Lidiane S Campos; Rachel P Guimarães; Paula Azevedo; Brunno M Campos; Augusto C Amato-Filho; AnelyssaD'Abreu.

2) Statistical analysis

A. Design: Juliana R Zuiani; AnelyssaD'Abreu; Brunno M Campos; Rachel P Guimarães; Fernando Cendes.

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C. Review and critique: AnelyssaD'Abreu; Joseph H Friedman; Brunno M Campos; Rachel P Guimarães; FernandoCendes.

3) Manuscript

A. Writing of the first draft: Juliana R Zuiani; Anelyssa D' Abreu.

B. Review and critique: AnelyssaD'Abreu; Joseph H Friedman; Fernando Cendes; Luiza G Piovesana; Lidiane S Campos; Rachel P Guimarães; Paula Azevedo; Brunno Campos; Augusto C Amato-Filho.

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