Diffusion Tensor Imaging of Vascular Parkinsonism

Structural Changes in Cerebral White Matter and the Association With Clinical Severity

Han-Cheng Wang, MD; Jung-Lung Hsu, MD; Alexander Leemans, PhD

Objective: To investigate the white matter (WM) microstructure using diffusion tensor imaging in patients with vascular parkinsonism (VP) and specific fiber tract involvement with respect to clinical severity.

Design: Diffusion measures (fractional anisotropy and mean diffusivity) were calculated from diffusion tensor images of patients with VP and control subjects. We performed global-, voxel-, and tract-based analyses to compare WM microstructural properties between groups. We further correlated findings with Unified Parkinson’s Disease Rating Scale scores and modified postural instability gait difficulty (PIGD) scores to identify most relevant tract involvement.

Setting: Shin-Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan.

Participants: Twelve patients with VP and 12 age-matched healthy controls without VP.

Results: In the VP group, the left thalamus, right frontal subcortical WM, and left anterior limb of the internal capsule had a significantly lower regional fractional anisotropy compared with the control group. The bilateral frontal subcortical WM showed a significantly higher regional mean diffusivity. The diffusion metrics in these regions were significantly correlated with the modified PIGD score part III, and the sum of modified PIGD scores parts II and III. Tract-based analysis showed a group difference in mean fractional anisotropy and mean diffusivity for multiple fiber bundles, but only diffusion measures of fiber tracts from the bilateral frontal lobe that pass through the anterior limb of internal capsule and tracts of the genu of the corpus callosum showed significant correlation with these scores.

Conclusions: Disruption of the microstructural organization of frontal lobe WM is associated with the severity of VP. Our findings are in accordance with the frontal lobe disconnection hypothesis for gait problems and reinforce the paradigm that the involvement of fibers related to the prefrontal cortex is crucial for the core features of VP.

Transverse diffusivity ($\lambda_2 + \lambda_3/2$), axial diffusivity ($\lambda_1$), and the degree of diffusion anisotropy (eg, the fractional anisotropy [FA]). Without barriers, water molecules move uniformly in all directions, which results in isotropic diffusion. By contrast, in the presence of barriers, such as cell membranes, nerve fibers, or myelin sheaths, the diffusion rate is typically larger in one direction than in another, which is then referred to as anisotropic diffusion. Being quantitative in nature, these DTI-based measures are more sensitive to tissue abnormalities than the typical visual evaluation of WM hyperintensities observed in conventional MRI data. To date, DTI studies have revealed WM alterations through measurements of decreased FA and/or increased MD in a variety of conditions, including aging, multiple sclerosis, schizophrenia, traumatic brain injury, amyotrophic lateral sclerosis, and Alzheimer disease. For an in-depth discussion of DTI and a more detailed description of several diffusion metrics (eg, FA and MD), we refer the interested reader to a recent review by Tournier et al.

We used parts II and III of the Unified Parkinson’s Disease Rating Scale (UPDRS) for the assessment of clinical severity of parkinsonian symptoms and signs in the patients and for comparison in the controls. In addition, for a better assessment of symptoms and signs related to gait, posture, and balance in general, we isolated items from total UPDRS and present these scores as modified postural instability gait difficulty (PIGD) scores. The modified PIGD score part II is derived from the sum of UPDRS items 2.11 (getting out of bed, a car, or a deep chair), 2.12 (walking and balance), and 2.13 (freezing) from part II. The modified PIGD score part III is derived from the sum of UPDRS items 3.9 (arising from chair), 3.10 (gait), 3.11 (freezing of gait), 3.12 (postural stability), 3.13 (posture), and 3.14 (global spontaneity of movement). We included items relevant to walking, posture, and shifting of postures, which contain more items than the original PIGD score. Clinical assessment for all VP patients was performed after discontinuing all antiparkinsonian drug therapy for more than 12 hours.

METHODS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PATIENTS WITH VP

Twelve patients with VP (aged 65-84 years; mean age, 75 years; 9 men and 3 women) were included in this study. All patients fulfilled the diagnostic criteria for VP proposed by Zijlmans et al. The criteria are (1) parkinsonism, defined as the presence of bradykinesia and at least 1 of the following: rest tremor, muscular rigidity, or postural instability; (2) cerebrovascular disease, defined by evidence of relevant cerebrovascular disease by CT or MRI findings or the presence of focal signs or symptoms that are consistent with stroke; (3) a relationship between the parkinsonism and the cerebrovascular disease; and (4) the absence of exclusion criteria, such as a history of repeated head injury, definite encephalitis, neuroleptic treatment, cerebral tumor or communicating hydrocephalus, or another alternative explanation for parkinsonism. Four of the 12 VP patients also met the DSM-IV criteria for the diagnosis of dementia based on a detailed history and neurological examination, whereas none of the controls showed abnormality in any of these cognitive deficits.

Twelve age-matched healthy volunteers were included in the control group (aged 64-79 years; mean age, 71 years; 8 men and 4 women). They were not taking any medication. Written informed consent in accordance with the requirements of the Declaration of Helsinki and the University of Magdeburg Ethical Committee was obtained from all participants before the study.

MRI ACQUISITION

All participants underwent whole-brain MRI (Achieva 3.0T; Philips Healthcare) within 1 week after the clinical examination. First, we acquired transaxial T2-weighted scans (repetition/echo times [TR/TE], 3000/90 milliseconds; number of excitations [NEX], 1; voxel size, $0.6 \times 0.6 \times 5 \text{ mm}^3$), fluid-attenuated inversion recovery images (TR/TE, 8000/120 milliseconds; inversion time, 2400 milliseconds; NEX, 1; voxel size, $0.7 \times 0.9 \times 5 \text{ mm}^3$), and high-resolution sagittal T1-weighted images (TR/TE, 7.04/3.44 milliseconds; NEX, 1; voxel size, $1.0 \times 1.0 \times 1.0 \text{ mm}^3$) were acquired.

Table 1. Demographic and Clinical Characteristics of Patients With Vascular Parkinsonism

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Abbreviations: −, negative; +, positive.
First, we acquired single-shot spin-echo echo-planar whole-brain DTI scans axially with a fat suppression sequence (TR/TE, 1000/70 milliseconds; 2-mm section thickness without gap; section acquisition matrix, 128 × 128 with 256 × 256-mm² field of view; 6/8 partial Fourier; NEX, 1; 80 sections; 32 gradient directions with a b value of 800 s/mm², and 1 image with a b value of 0 s/mm²). Then, we performed post-processing steps, each data set for each individual consists of the clinical severity and the global DTI indices in the patient group, controlling for age effects). To investigate the relationship between the clinical severity and the global DTI indices in the patient group, we used the linear regression model with age as a covariate.

- **Table 2. Mean Global FA and MD Values in VP Patients and Controls**

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<thead>
<tr>
<th>Group</th>
<th>Mean Global FA</th>
<th>Mean Global MD</th>
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<td>VP</td>
<td>0.38 (0.02)</td>
<td>103 (4.5)</td>
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<tr>
<td>Control</td>
<td>0.42 (0.03)</td>
<td>93.7 (6.7)</td>
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**Abbreviations:** FA, fractional anisotropy; MD, mean diffusivity; PIGD, postural instability gait difficulty; UPDRS, Unified Parkinson’s Disease Rating Scale; VP, vascular parkinsonism.

**IMAGE PROCESSING**

The DTI-based preprocessing steps performed in this work have been described previously in detail. In summary, we took the following steps:

1. All DTI data sets were corrected for eddy current–induced geometric distortions and subject motion.
2. The diffusion tensor model was fitted to the data with a graphical toolbox (ExploreDTI; http://www.exploredti.com/) using a nonlinear regression method. The diffusion measures (FA and MD) were subsequently computed.
3. A population-based DTI atlas in Montreal Neurological Institute space was used to drive the tensor-based affine and nonaffine coregistration techniques. At the final transformation step, the “preservation of principal direction” strategy was applied to reorient the diffusion tensor. This coregistration approach has already been applied successfully in a wide range of applications, where adjusting for morphological intersubject (and intergroup) differences such as ventricle size is considered necessary. After finishing these DTI-based preprocessing steps, each data set for each individual consists of the spatial normalized DTI scans and the derived diffusion measures FA and MD, which can be used for further statistic analysis.

**GLOBAL ANALYSIS**

In summary, the intracranial brain was extracted from the image where the b value is 0 s/mm² from normalized data set with the brain extraction tool from the FMRIB Software Library (BET2; http://www.fmrib.ox.ac.uk/fsl/). The brain was further subdivided into regions of cerebrospinal fluid and brain tissue (combined gray matter and WM) by segmenting all cerebrospinal fluid voxels using an automated gray-level thresholding method, performed on the MD map. For each subject, the mean global FA and MD of brain tissue were calculated and potential group differences were examined with a 2-way analysis of variance (controlling for age effects). To investigate the relationship between the clinical severity and the global DTI indices in the patient group, we used the linear regression model with age as a covariate.

**VOXEL-BASED ANALYSIS**

In addition to the global analysis, we performed a whole-brain voxel-based analysis using the statistical parametric mapping (SPM8) toolbox to search for brain regions with significant differences in FA and MD between the VP patients and controls. After applying spatial smoothing (8-mm isotropic gaussian kernel), the general linear model in SPM (2-sample t test) with age as a covariate was applied to assess potential differences between the 2 groups. The results of this analysis were t statistic images, which were subsequently thresholded at t ≥ 2.83 (corresponding to the level of P < .005). Cluster sizes larger than 64 voxels and corrected familywise error P values smaller than .05 were considered significant after correction for multiple independent comparisons. To study the potential FA (or MD) differences between VP patients and controls in more detail, an image mask from the regions with significant FA (or MD) differences...
was created and applied to the each individual’s FA (or MD) image. The mean FA (or MD) value within these regions of interest was used to search for the potential correlation with total UPDRS scores or modified PIGD scores with age as the covariate not of interest. The significant P value was set to .05.

TRACT-BASED ANALYSIS

To explore the relationship between the clinical severity and the involvement of specific fiber tracts, we calculated the DTI variables within the selected fiber tracts. Seven fiber tracts (tracts passing genus of the corpus callosum [ACC], tracts from the frontal lobe through the anterior limb of the internal capsule [ALIC], tracts from the premotor area to the brainstem [Premotor], tracts from the motor cortex to the brainstem [Pyramidal], tracts from the supplementary motor area to the brainstem [SMA], arcuate fasciculus [AF], superior longitudinal fasciculus [SLF], and tracts passing the splenium of the corpus callosum [PCC]) were reconstructed for each hemisphere using a deterministic streamline fiber tractography approach as implemented in the DTI graphical toolbox (FA threshold, 0.2; step size, 1 mm; angle threshold, 45°) (Figure 1). The ACC, ALIC, premotor, pyramidal, and SMA tracts were used as motor-related tracts for clinical correlation. The AF, SLF, and PCC tracts were used as non–motor-related tracts for comparison. We used linear regression with age as a covariate to examine the between-group difference and the correlation between total UPDRS scores and modified PIGD scores and DTI variables in each fiber tract within the VP patient group. We considered P values smaller than .05 to be significant.

RESULTS

GLOBAL ANALYSIS

With a 2-way analysis of variance (correcting for age effects), we observed a significant group difference between the mean global DTI measurements. The mean (SD) global FA values in the VP group were significantly lower than in the control group (0.38 [0.02] vs 0.42 [0.03] with age-adjusted group difference of P = .02). The mean (SD) global MD values in the VP group were significantly higher than in the control group (101.3 [4.5] × 10⁻⁵ mm²/s vs 93.7 [6.7] × 10⁻⁵ mm²/s with age-adjusted group difference of P = .01). Mean global FA and MD values and UPDRS results are summarized in Table 2.

REGIONAL (VOXEL-BASED) ANALYSIS

Seven clusters of significantly lower regional FA in VP were distributed on the bilateral anterior limb of internal capsule, bilateral thalamus, and bilateral frontal subcortical WM. After corrected multiple comparison using familywise error, 3 clusters of significantly lower regional FA were found in the VP group compared with the controls. These regions included the left thalamus (cluster size, 1896 mm³), the right frontal subcortical WM (cluster size, 8056 mm³), and the left anterior limb of the internal capsule (cluster size, 3784 mm³). No significantly higher regional FA cluster was found. Results of MD analysis showed 2 clusters of significantly higher regional MD in VP group compared with controls, that is, the left frontal subcortical WM (cluster size, 2536 mm³) and the right frontal subcortical WM (cluster size, 8680 mm³). No significantly lower regional MD cluster was found (Figure 2). The mean FA values from significantly lower FA regions in VP patients correlated with the modified PIGD score part III (P = .001; adjusted R² = 0.77) and the sum of modified PIGD score parts II and III (P = .009; adjusted R² = 0.65) with age as the covariate not of interest (Figure 3A-B). The mean MD values from significantly higher MD regions in VP patients correlated...
correlated with the modified PIGD score part III (P = .04; adjusted R^2 = 0.51) and the sum of modified PIGD score parts II and III (P = .03; adjusted R^2 = 0.55) with age as the covariate not of interest (Figure 3C-D). Mean FA and MD values did not correlate with total UPDRS score part II or part III or their sum.

TRACT-BASED ANALYSIS

For the tract-based analysis, the group differences of mean FA and MD values using age as the covariate not of interest are presented in Table 3 and Table 4. The mean FA values of the fiber tracts from the ALIC in bilateral hemispheres showed a significantly negative correlation with the modified PIGD score part III (P = .02; R^2 = 0.59) and with the sum of modified PIGD score parts II and III (P = .03; R^2 = 0.54). No significant correlations were found between the FA and the total UPDRS score part II or part III or their sum (Figure 4A-B). Mean FA values from other tract regions (ACC, premotor, pyramidal, SMA, AF, SLF, and PCC) did not show any significant correlation with any of the total UPDRS scores or the modified PIGD scores. Mean MD values from the region of fibers tracts passing through the ACC showed a significantly positive correlation with the modified PIGD score part III (P = .01; R^2 = 0.61) (Figure 4C). No significant correlations were found between the MD and any of the total UPDRS scores or modified PIGD scores for other tracts.

Vascular parkinsonism accounts for a sizable proportion of parkinsonism. In a study from Spain, VP accounted for 4.4% of all cases of parkinsonism. In a population-based Italian study, 8 of 68 incident cases of parkinsonism (12%) were diagnosed as VP. These figures may be underestimated. In an autopsy study of the 5 patients with parkinsonism found to have vascular disease at autopsy, none had been given the clinical diagnosis of VP. That study, however, had only 39 autopsied brains available for analysis and was retrospective, with clinical diagnosis based on the medical records reviewed by a neurologist.
Vascular parkinsonism is distinct from PD in terms of imaging findings and clinical features. Nearly all VP patients have structural MRI and/or CT abnormalities, mainly multiple deep subcortical lesions, in contrast to only a minority of patients with PD showing subcortical WM lesions.\(^1\) Dopamine transporter imaging can also distinguish VP patients from those with PD. Although it has been shown that the mean striatal iodine 123-iodoamphetamine uptake is lower in VP patients than in healthy controls,\(^5\) several studies have shown that the striatal uptake ratio is much lower in PD than in VP.\(^5\) In a clinicopathologic study, pigmented neurons in the substantia nigra in VP were found to be preserved from ischemic changes.\(^9\) These differences suggest that the pathophysiology of VP is distinct from the typical presynaptic dopaminergic deficit found in PD.

Although diffuse subcortical WM lesions are the principal pathological changes seen in VP,\(^2,6,8,9,54\) how these changes lead to parkinsonism in certain patients and not in others remains unclear. The lack of specificity for distinguishing VP from other pathological conditions is also evident from other studies. Hu et al\(^5\) demonstrated that the vascular lesion load did not differ between atypical and typical parkinsonism on MRI. Yamanouchi and Nagura\(^6\) compared brain pathology in 24 VP patients with that in 22 age-matched patients with Binswanger disease who had no parkinsonism. The authors found no significant difference in the extent of vascular lesions at the basal ganglia between VP patients and their Binswanger disease comparison group without parkinsonism.

The localization of WM pathology and its involvement with respect to specific tracts might be more crucial for developing parkinsonism than its overall extent as determined by lesion load, for example. This view cannot be tested directly with traditional neuroimaging techniques, because they are not able to delineate specific WM fiber bundles. Diffusion tensor imaging, a novel, noninvasive MRI technique capable of providing quantitative measures of the microstructural organization of WM pathways, on the other hand, can serve such purposes.\(^16,53\)

In this study, we showed that VP is associated with structural abnormalities of the WM architecture. Regional (voxel-based) intergroup analysis showed significantly lower regional FA and significantly higher regional MD in the left thalamus, the left anterior limb of the internal capsule, and bilateral frontal subcortical WM, after corrected multiple comparison using familywise error. This asymmetric pattern could be owing to our relatively small case number and may not be generalizable to all patients with VP. The anterior limb of the internal capsule contains fibers connecting the cortex with the corpus striatum, fibers connecting the lentiform and caudate nuclei, and fibers running from the thalamus to the frontal lobe. These WM pathways and the thalamus are all closely associated with movement control. When looking into the microstructural organization of these fiber tracts, we found abnormal diffusion properties for motor-related and non–motor-related tracts. Because VP patients mostly have extensive global WM changes on their conventional brain images, as was the case for our patients, most tracts would appear to be disrupted with tract-based analysis. However, when we correlate DTI variables with clinical severity, only the anterior fiber tracts (ALIC and ACC) showed significant correlations.

Our results did not show any correlations between WM microstructural properties and total UPDRS scores part II or part III or the sum of parts II and III. To some extent, this finding is expected. Although the UPDRS has been routinely used for the assessment of clinical severity in PD, it contains many items related to limb tremor, rigidity, and hand dexterity. In the case of VP, patients tend to have less limb rest tremor, rigidity, and hand dexterity than in PD, while having more postural and gait problems.\(^1,2,56\) Consequently, we believe that the full set of total UPDRS scores is not an adequate measure for assessing VP severity. On the other hand, the modified PIGD scores that we have used measure falls, posture, shifting of postures, gait, and balance and better reflect the clinical severity of VP. The modified PIGD score part III and the sum of modified PIGD scores parts II and III correlated with the WM diffusion properties of the left thala-

**Figure 4.** Correlation between the Unified Parkinson’s Disease Rating Scale modified postural instability gait difficulty (PIGD) scores and diffusion tensor imaging variables for specific white matter fiber bundles. A, Mean fractional anisotropy (FA) of the tracts from the frontal lobe passing through the anterior limb of the internal capsule ($0.55 \times 0.0015 \times \text{age} - 0.015 \times \text{modified PIGD score part III}$) vs the modified PIGD score part III ($P = 0.02; R^2 = 0.59$). B, Mean FA of the tracts from the frontal lobe passing through the anterior limb of internal capsule (0.59 + 0.0015 \times \text{age} - 0.011 \times \text{modified PIGD score parts II and III}) vs the modified PIGD score parts II and III ($P = 0.03; R^2 = 0.54$). C, Mean mean diffusivity values of the tracts that pass through the genu of the corpus callosum ($5.9 \times 10^{-5} + 1.83 \times 10^{-6} \times \text{age} + 5.05 \times 10^{-3} \times \text{modified PIGD score part III}$) vs the modified PIGD score part III ($P = 0.01; R^2 = 0.61$).

\(^{1,2,6,8,9,54}\)
musr, the left anterior limb of the internal capsule, and bilateral frontal subcortical WM in the regional (voxel-based) intergroup analysis. In the tract-based analysis, similar associations were found for ALIC and ACC. By contrast, the microstructural properties of fibers corresponding to the traditional motor-related cerebral cortex (premotor, pyramidal, or SMA) did not correlate with clinical severity. These findings suggest that, although traditionally attributed to cognitive function, the basal ganglia loops involving the prefrontal cortex are more closely related to VP symptoms than those involving the motor-related areas.

The major clinical deficits of VP consist of balance and gait problems. Increasing evidence suggests an important role of cognitive factors such as executive function and attention in the control of balance during standing and walking. Matsui et al. found decreased resting regional cerebral blood flow in the bilateral orbitofrontal cortex in 24 PD patients with freezing of gait compared with 31 PD patients without freezing of gait. In another study of anticipation, preparation, and execution of foot movements using functional MRI, anterior prefrontal regions appeared to be involved in the decision to move and the movement expectation. Many studies have shown that gait in PD is more dependent on focused attention and external cues. Frontal cortex may play a crucial role in controlling gait patterns. Dysfunctional frontal areas could lead to decreased ability to focus attention on a motor program and to continue this program when other stimuli need to be integrated. In this regard, the gait problems in PD can be seen as an attention problem.

Our study is, to our knowledge, the first in vivo study confirming the association between microstructural properties of cerebral WM and symptoms and signs of VP. In particular, we have shown the involvement of specific tracts, namely fibers linked to the prefrontal cortex, because we observed a strong correlation between the diffusion properties of these pathways and the clinical severity of symptoms and signs consisting mainly of gait, balance, and fall problems. Despite this interesting finding, we should acknowledge several limitations of this study. First, our sample size (12 in each group) is relatively small. Second, we compared DTI variables between VP patients and healthy controls, but did not study patients with apparently similar vascular WM lesions who do not have parkinsonian symptoms. With the latter patient group, it would be feasible to better understand the selectivity of tract involvement in VP patients. Third, voxel-based analyses require spatial correspondence between the images, which is usually not guaranteed. In addition, although typically assumed to be negligible, the amount and type of smoothing, coregistration settings of variables, and choice of atlas/template space may affect the results of these analyses. Finally, interpretation of DTI findings can be complicated by partial volume effects and complex WM fiber architecture that cannot be characterized adequately by the second-rank diffusion tensor framework. An ongoing prospective cohort study on WM changes and development of VP uses DTI as a part of the study protocol. We hope that this study will answer many questions regarding the causes and consequences of cerebral small vessel disease, including VP.

In conclusion, we have demonstrated that microstructural WM tract abnormalities of the frontal lobe are associated with the severity of VP. Our findings are in line with the frontal lobe disconnection hypothesis for gait problems, and can explain the differentiation in characteristics of VP compared with PD. As such, we believe that WM lesions disrupting the motor-related pathways of the corticostriatal loops may produce certain parkinsonian symptoms and that the involvement of WM fiber bundles related to the prefrontal cortex is more important in producing the core features of VP.


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REFERENCES


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