A Whole-Brain Analysis in De Novo Parkinson Disease


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BACKGROUND AND PURPOSE: Widespread cerebral changes are observed in advanced stages of Parkinson disease (PD), suggesting that PD is a multisystem disorder. We investigated with MR imaging whether global brain changes are present in early clinical stages of PD and correlated the findings with the type of clinical presentation.

MATERIALS AND METHODS: T1-weighted images and mean diffusivity and fractional anisotropy (FA) maps calculated from diffusion tensor imaging (DTI) were obtained in 27 patients with de novo drug-naïve PD, who were classified according to the clinical features in tremor-dominant type (n = 13), akinetic-rigid type (n = 11), and mixed type (n = 3). Sixteen healthy subjects provided control data. With SIENAX software, total brain, gray matter (GM), and white matter (WM) volumes were computed from T1-weighted images, whereas brain histograms were obtained from mean diffusivity and FA maps.

RESULTS: Total brain, GM and WM volumes were not significantly different in patients as a whole or subgroups and controls. As compared with controls, patients with PD as a whole and patients with the akinetic-rigid type showed an increase (P ≤ .01) of the twenty-fifth percentile of the FA histogram. In patients with the akinetic-rigid type, there also was a trend toward an increase of the mean and fiftieth and seventy-fifth percentiles, and a reduction of the skewness of the FA histogram. Patients with tremor-dominant type showed a trend toward an increase of the twenty-fifth percentile of the FA histogram.

CONCLUSIONS: In patients with de novo PD, there is an increase of FA values, more pronounced in patients with the akinetic-rigid type, probably reflecting diffuse subtle GM loss. This is in line with the hypothesis that widespread neurodegeneration is already present at the time of the clinical onset.
a supportive criterion for the diagnosis of idiopathic PD. Moreover, all patients were screened for cardiovascular autonomic dysfunction and cognitive impairment. Signs of autonomic failure, Mini-Mental State Examination scores ≤24/30,26 significant medical conditions, and previous therapies with antiparkinsonian drugs were considered as exclusion criteria.

Sixteen healthy volunteers (7 women and 9 men; mean age, 59.4 ± 9.4 years), recruited among personnel working at the MR imaging unit and their relatives, served as controls. They were of the same socioeconomic and educational level, and significant (P < .05) differences between patients and controls for sex (χ² test) and age (Mann Whitney U test) were not observed. All patients and healthy subjects gave their informed consent to participate in the study, which was approved by our institutional review board.

Motor Evaluation. Severity of parkinsonism was evaluated by the Unified Idiopathic Parkinson’s Disease Rating Scale (UPDRS),27 and the Hoehn and Yahr staging.28 On the basis of the predominant motor features in UPDRS, patients were subtyped into 1 of 3 clinical classes and a quadrature head coil.

All examinations were performed on a 1.5T system (Magnetom Symphony; Siemens, Erlangen, Germany) equipped with 30 mT/m gradients and a quadrature head coil.

MR Imaging. After scouts, the examination protocol included axial high-resolution contiguous 3D T1-weighted images, which were obtained with a magnetization-prepared rapid acquisition of gradient echo sequence (TR = 2500 ms, TE = 3.7 ms, TI = 730 ms, flip angle = 15°, section thickness = 1 mm, FOV = 256 mm, matrix size = 256 × 256, NEX = 1), and axial T2-weighted images, which were obtained with a fluid-attenuated inversion recovery (FLAIR) sequence (TR = 9000 ms, TE = 114 ms, TI = 2500 ms, section thickness = 4 mm, FOV = 230 mm, matrix size = 256 × 256, turbo factor = 21, NEX = 1).

DTI. A diffusion-weighted single-shot echo-planar imaging sequence (TR = 6000 ms, TE = 95 ms, section thickness = 5 mm, FOV = 256 mm, matrix size = 128 × 128) was acquired on an axial plane with diffusion-sensitizing gradients applied along 6 noncollinear directions [(1,0,1), (−1,0,1), (0,1,1), (0,1,−1), (1,1,0), (−1,1,0)] by using a b-value of 0 (b₀ image) and 1000 s/mm². To improve the signal-to-noise ratio, we obtained 8 averaged acquisitions for each DTI image. Maps of mean diffusivity and FA were calculated from the DTI after both automatic segmentation of the brain from the nonbrain tissue and eddy currents correction by means of FDT 1.0 (FMRIB’s Diffusion Toolbox 1.0)29 part of FSL 3.3 (FMRIB Image Analysis Group, Oxford, UK).30

### Table 1: Demographic and clinical data in patients with de novo Parkinson disease

<table>
<thead>
<tr>
<th></th>
<th>Whole PD (n = 27)</th>
<th>TDT (n = 13)</th>
<th>ART (n = 11)</th>
<th>MT (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at exam (years ± SD)</td>
<td>60.9 ± 9.7</td>
<td>57.9 ± 10.4</td>
<td>62.2 ± 8.3</td>
<td>68.3 ± 7.7</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18</td>
<td>8</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Disease duration (months ± SD)</td>
<td>17 ± 7.4</td>
<td>16.5 ± 5</td>
<td>17.5 ± 3.3</td>
<td>18 ± 10.3</td>
</tr>
<tr>
<td>UPDRS (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subitem II</td>
<td>6.0 ± 4.0</td>
<td>3.6 ± 2.0</td>
<td>7.0 ± 3.4*</td>
<td>13.0 ± 3.0</td>
</tr>
<tr>
<td>Subitem III</td>
<td>12.7 ± 8.3</td>
<td>7.3 ± 3.6</td>
<td>15.8 ± 8.0*</td>
<td>24.3 ± 0.5</td>
</tr>
<tr>
<td>Hoehn and Yahr (mean ± SD)</td>
<td>1.2 ± 0.4</td>
<td>1.0 ± 0.1</td>
<td>1.4 ± 0.4*</td>
<td>1.8 ± 0.2</td>
</tr>
</tbody>
</table>

### Image Analysis

**Visual Assessment.** Two operators with more than 10 years of clinical experience (C.T. and M.M.) jointly evaluated T1-weighted images and FLAIR MR images to exclude patients with extensive white matter (WM) signal-intensity changes, defined as a score >2 on a 0–6 visual scale,33 and those with secondary parkinsonism. Moreover, they excluded from further analysis patients with overt motion artifacts in the DTI.

**Total Brain, GM, and WM Volumes.** Brain volumes were measured by using the SIENAX software extensively described elsewhere.24 Briefly, brain was first segmented from nonbrain tissue by using a brain-extraction tool of FSL 3.3. The brain images were affine-registered to MN1152 (Montreal Neurological Institute, Montreal, Canada) space (by using the skull image to determine the registration scaling); this is primarily to obtain a volumetric scaling factor to be used as a normalization for head size. Finally, brain images were segmented, and the total brain, GM, and WM volume values, normalized for head size of the subject, were calculated.

**Whole-Brain Histograms of Mean Diffusivity and FA.** The methods for histogram analysis were reported previously.32 Preliminarily, motion artifacts and eddy current distortions in the source DTIs were corrected by using the FTD software implemented in the FSL package.30 Then, to segment brain parenchyma from CSF, for each b₀ image we created a binary brain mask by using the FAST (FMRIB’s Automated Segmentation Tool 3.53, part of FSL 3.3)35 2 classes segmentation function. This mask was applied in MRicro36 on mean diffusivity and FA maps for voxel-by-voxel data extraction. We generated histograms of mean diffusivity and FA, normalizing each bin to the total number of voxels contributing to the histogram. The mean; twenty-fifth, fiftieth (median), and seventy-fifth percentile values; skewness and kurtosis of the whole-brain mean diffusivity; and FA histograms were computed by using a custom-made Matlab (Matlab 6.5 R13; MathWorks, Natick, Mass) program.
Table 2  Normalized GM, WM, and total brain volumes

<table>
<thead>
<tr>
<th></th>
<th>GM</th>
<th>WM</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>782 ± 41</td>
<td>713 ± 65</td>
<td>1495 ± 81</td>
</tr>
<tr>
<td>PD Patients</td>
<td>773 ± 55</td>
<td>718 ± 49</td>
<td>1491 ± 89</td>
</tr>
<tr>
<td>ART-PD</td>
<td>767 ± 54</td>
<td>720 ± 36</td>
<td>1487 ± 79</td>
</tr>
<tr>
<td>TDT-PD</td>
<td>776 ± 62</td>
<td>722 ± 55</td>
<td>1500 ± 104</td>
</tr>
</tbody>
</table>

Note:—TDT indicates tremor-dominant type; ART, akinetic-rigid type; GM, gray matter; WM, white matter.

* Volume values (cubic centimeters) are reported as mean ± SD.

Statistical Methods

The nonparametric Mann Whitney U test was used to compare the total brain, GM, and WM volumes and histogram-derived metrics of mean diffusivity and FA between patients with PD as a whole and controls and between patient clinical subgroups and controls. Because of the small number of patients with mixed type of clinical presentation, they were excluded from the subgroups analysis.

To correct for multiple comparisons, we considered a P value ≤ .01 statistically significant, a P value between .01 and .05 was considered as a trend, and P values > .05 were considered not significant.

Correlations between the parameters that resulted in a significant difference or showed a trend, and the clinical motor scores (UPDRS item II and III) and disease duration were assessed by using the statistical Spearman rank testing.

Results

Few small focal lesions of the cerebral WM were observed in 11 patients and 7 controls.

Brain volumes and mean diffusivity and FA histogram data in patients and controls are detailed in Tables 2–4 and shown in Fig 1. No significant differences were found for total brain, GM, and WM volumes and histogram-derived mean diffusivity metrics between controls and the whole group of patients with PD or any subgroup of patients with PD. The twenty-fifth percentile of the FA histograms was significantly (P = .009) higher in the whole group of patients than in controls (Fig 2). A significant (P = .006) increase of the twenty-fifth percentile of the FA histograms as compared with controls was also observed in patients with akinetic-rigid type PD, which was accompanied by a trend for an increase of the mean (P = .043), fiftieth percentile (P = .026), and seventy-fifth percentile (P = .029) and for a reduction of the skewness (P = .033) of the FA histograms. In patients with tremor-dominant type PD, there was a trend (P = .045) for an increase of the twenty-fifth percentile of the FA histograms as compared with controls.

Correlations

No significant correlation between FA histogram-derived metrics and clinical scores and disease duration was found in the whole group of patients with PD or in any PD subgroup.

Discussion

Despite several cross-sectional and longitudinal MR imaging studies,8-12,35-41 the distribution and progression of brain atrophy in PD are not yet established. In particular, recent studies that used voxel-based analysis of the mean apparent diffusion coefficient, no evidence of brain-tissue damage was found in patients with PD except an isolated increase of diffusivity in the olfactory tracts.47

Overall, previous MR imaging studies assessing global or regional atrophy were performed on patients in relatively advanced stages of the disease. To the best of our knowledge, this is the first study in which cross-sectional global measurements of atrophy and mean diffusivity and FA of water protons were performed to detect possible subtle changes of the brain in patients with de novo PD.

For assessment of brain volumes, we used SIENAX, which is the cross-sectional version of SIENA (Structural Image Evaluation, by using Normalization, of Atrophy; available at http://www.fmrib.ox.ac.uk/fsl) software, a fully automated, robust, and accurate method of longitudinal analysis designed to estimate global brain atrophy. It provides measures of total brain, GM, and WM volumes normalized for head size of the subject and has been used in normal aging,48 multiple sclerosis,49 and neurodegenerative50 and vascular disease.51 In recent years, histogram analysis of whole-brain MR images ex-
exploring different tissue parameters reflecting microstructure of the nervous tissue, including apparent diffusion coefficient calculated from diffusion-weighted imaging or mean diffusivity and FA maps calculated from DTI, was proposed to get a global assessment of brain damage in diffuse or multifocal diseases, such as multiple sclerosis, neurodegenerative disorders, and leukoaraiosis.21-23,52,53 The whole-brain volume and global assessment of brain damage in diffuse or multifocal diseases, such as multiple sclerosis, neurodegenerative disorders, and leukoaraiosis.21-23,52,53 The whole-brain volume and intensity and FA maps calculated from DTI, was proposed to get a global assessment of brain damage in diffuse or multifocal diseases, such as multiple sclerosis, neurodegenerative disorders, and leukoaraiosis.21-23,52,53 The whole-brain volume and global assessment of brain damage in diffuse or multifocal diseases, such as multiple sclerosis, neurodegenerative disorders, and 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sclerosis, neurodegenerative disorders, and leukoaraiosis.21-23,52,53 The whole<br>Table 3: Mean diffusivity histogram parameters*<br><br>Table 4: FA histogram parameters*<br><br>Note:—TDT indicates tremor-dominant type; ART, akinetic-rigid type.<br>* Mean diffusivity values (10^-3 mm^2/s) are reported as mean ± SD.
neuro-rigid type may be considered a risk factor for development of dementia in PD. In our sample, patients with akinetic-rigid type showed higher UPDRS and Hoehn and Yahr scores than patients with the tremor-dominant type. Hence, it is possible that our results merely reflect the severity of the clinical scores rather than differences between subtypes. However, FA values did not correlate with UPDRS and Hoehn and Yahr scores in our series. On the other hand, in large epidemiologic studies, patients with new-onset akinetic-rigid type tended to have higher UPDRS and Hoehn and Yahr scores than patients with tremor-dominant type, confirming a more severe impairment already at this early clinical stage. Our results seem to indicate that patients with akinetic-rigid type might have a more severe brain involvement than patients with tremor-dominant type in an early stage of the disease. Further longitudinal studies in larger sample sizes are required to address this issue and to ascertain whether these abnormalities are predictive of the clinical-pathologic evolution, and notably of the development of cognitive impairment.

We recognize some limitations of our study. First, we examined a relatively small number of patients in whom no correlation between the MR imaging measurements and severity of the clinical motor features was found. Hence, our results have to be considered as preliminary to future studies on larger samples of patients whose motor and cog-
positive performances need to be evaluated and correlated with the MR imaging data. Second, we used a DTI protocol with relatively thick sections and only 6 directions for computation of DT. Optimized protocols with thinner sections and more directions could improve quantification of the tissue structure evaluation with DTI. Finally, with the present approach, we could not establish whether the observed subtle loss of GM in patients with PD was due to generalized or regional changes.

Conclusion

Our study indicates that total, GM, and WM volumes as calculated with SIENAX are not significantly decreased in patients with de novo PD. However as compared with age-matched controls, patients with PD as a whole and patients with akinetic-rigid type show an increase of the twenty-fifth percentile of the FA histogram. This finding is consistent with the hypothesis that subtle GM loss is present in patients with PD since the early clinical phases and that this feature is more pronounced in patients with akinetic-rigid type.

References