Imaging Brain Iron and Diffusion Patterns:

A Follow-up Study of Parkinson's Disease in the Initial Stages

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Rationale and Objectives: The aim of this study was to examine changes of brain iron content and diffusion patterns longitudinally in early-stage Parkinson's disease (PD) patients using T2- and T2*-based magnetic resonance imaging (MRI) over 2-year follow-up.

Materials and Methods: We imaged 32 PD patients with tremor and 19 healthy controls. A follow-up study (median 25 months, range 22–31 months) was accomplished for 25 patients (men:women = 11:14; age range 44–87 years, median 73 years). All patients and healthy volunteers underwent clinical, neuropsychological, and MRI examinations on the same day. Three different MRI sequences were used and their results were compared: T2-weighted imaging, susceptibility-weighted imaging, and T2* mapping. Additionally, we evaluated diffusion tensor data between groups using tract-based spatial statistics.

Results: Over the 2-year follow-up, the iron-related relaxation increased in the globus pallidus anterior and the caudate nucleus and slightly in the substantia nigra pars compacta (SNc). In the globus pallidus anterior and medial SNc, the change was associated with mild cognitive impairment. In the caudate nucleus, the increase was pronounced in patients with disease onset at 67 years or older. In the SNc, medial transverse relaxation was increased, and in the thalamus, it was decreased, in patients with PD compared with healthy volunteers at 2-year follow-up. Tract-based spatial statistical data did not differ between groups based on gender or Unified Parkinson's Disease Rating Scale, but a slight tendency to decreasing fractional anisotropy ($P < .10$) in the genu of corpus callosum and bilaterally in corona radiata was seen over 2 years.

Conclusions: PD-related changes were found in putative iron content over 2 years. Although mild in the initial stages, these changes were consistent over MRI sequences. Rather than correlating with disease duration, the rate of changes was associated with individual characters, such as cognitive decline and age.

Key Words: Brain iron; diffusion tensor imaging; magnetic resonance imaging; Parkinson's disease.

Parkinson's disease (PD) is a neurodegenerative disease that is characterized by tremor, rigidity, bradykinesia, and postural instability (1). These motor symptoms are the basis of the diagnosis. Although the disease is incurable, various treatment options are available to enhance the quality of life, and new neuroprotective agents are constantly being developed (1–3). Depending on treatment, early initiation of therapy may provide benefit for the patient (4). Therefore, early diagnosis and initiation of therapy including follow-up are urgently needed. An accurate diagnosis of PD is challenging and increasingly complemented by imaging (5,6).

Imaging findings in PD patients are limited, but slight changes may be found with improving imaging techniques. Imaging of PD patients has made the most progress in the area of imaging dopamine transporters using positron emission tomography and various techniques of magnetic resonance imaging (MRI) (5–7). In addition to spectroscopy, diffusion tensor imaging (DTI), and functional imaging, one of the aspects investigated with MRI is the brain iron content, which is increased in the substantia nigra pars compacta (SNc) of PD patients (5–11). The brain iron content is associated with the loss of dopamine, and their concentrations seem to correlate as earlier shown in putamen (12). Therefore, because diagnostically promising results on the loss of dopamine have been reported with positron emission tomography (5), the results may be indirectly repeated by imaging iron with nonionizing MRI.

Earlier cross-sectional studies have investigated the association between brain iron content increase and disease duration. Although the iron content in SNc is increased in comparison

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with healthy volunteers, this has not correlated with the duration of PD symptoms (8,13). However, in substantia nigra pars reticulata (SNr), the hypointense part of substantia nigra, the iron content may increase over time during disease progression (8), while with later-onset PD, the iron content may, in contrast to early onset, decrease (10). In the putamen, reduced iron content with disease duration has been found (14,15). Although these studies agree on the majority of findings, they might be prone to individual variations and hemispheric differences (16). To our knowledge, longitudinal studies are not available.

In DTI, fractional anisotropy (FA) indicates the degree of anisotropic orientation of water diffusion that is primarily induced by fiber tracts. FA can be processed by comparing two groups using tract-based spatial statistics (TBSS) (17–19). In healthy volunteers, FA usually decreases with age in white matter (WM) but may increase in gray matter (20). The relation between iron and DTI is unclear. The presence of iron in diffusion gradients may increase the measured signal decay; however, there may also be actual alterations in the tissue structure (20). In PD, the substantia nigra and frontal lobes show reduced FA in regions of interest (ROI) analysis (21,22). However, TBSS studies in this patient group are not found in literature.

The aim of this study was to investigate the brain iron accumulation longitudinally over 2-year period in patients with Parkinson's disease. The rate of such accumulation was compared with the patients' clinical and neuropsychological data. To potentially support these tests, similar comparisons with the same group comparisons were made for DTI data using TBSS.

MATERIALS AND METHODS

This study included 52 patients who were referred from local health centers to the university hospital with symptoms indicative of PD. The inclusion criterion was to present two or more of the common symptoms of PD: resting tremor, bradykinesia or hypokinesia, rigidity, or postural instability. Exclusion criteria included the presence of Alzheimer's disease or other dementia; other severe disease such as heart, lung, or gastrointestinal disease; hypofunction of liver or kidney; active cancer; neurological or psychiatric disease; a history of cerebrovascular attack; contraindications for MRI; alcohol or drug addiction; and pregnancy.

All patients underwent clinical investigation and neuropsychological testing. Based on such thorough clinical investigation, PD was diagnosed in 37 patients. For this study, we only selected PD patients with tremor, leaving 33 patients. The patients underwent MRI, during which one patient withdrew because of claustrophobia, leaving 32 patients for this study (age range 42–86 years, median 71 years; men:women = 15:17). Twenty-five of 32 patients (age range 44–87 years, median 73 years, men:women = 11:14) could be included in a 2-year follow-up including MRI (median 25 months, range 22–31 months). Clinical investigation included the evaluation of Unified Parkinson's Disease Rating Scale (UPDRS) and Mini-Mental State Examination (MMSE). Based on the neuropsychological assessment, patients were classified as having mild cognitive impairment (MCI) or as being cognitively intact (23).

The study also included 20 healthy volunteers. The inclusion criterion was a clinical neurological examination with no abnormal findings. The exclusion criteria were similar to those of the PD patients. One of the volunteers showed severe symptoms of dementia and was excluded, leaving 19 volunteers for this study (age range 58–80 years, median 65 years, men:women = 4:15). All subjects gave their informed consent for the study, and the study was approved by the hospital ethical committee.

MRI Protocol and Analysis

All MRI examinations were performed with a 3-T Siemens TrioTim (Siemens, Erlangen, Germany). The MRI protocol included 3-dimensional T2-weighted imaging (T2WI) using the sampling perfection with application optimized contrasts using different flip-angle evolution (single-slab, 3-dimensional, T2-weighted turbo-spin-echo sequence with high sampling efficiency) acquisition method (24), susceptibility-weighted imaging (SWI) (25,26), and T2$\star$ mapping (27,28). Additionally, we performed DTI with 20 gradient encoding directions, b value of 1000, and 0 s/mm^2. Imaging parameters are presented in Table 1. For the image analysis of the nonquantitative T2WI and SWI, we calculated the contrast, c, against the genu of the corpus callosum (gCC),

$$c = \frac{(S_a - S_{gCC})}{(S_a + S_{gCC})}$$

where S_a and S_{gCC} are the signal intensities of the concerned structure and gCC, respectively, as previously described in Rossi et al (29,30). In T2$\star$ mapping, the quantitative T2$\star$ (ms) was used. Representative images are shown in Figure 1.

Analysis for Iron Content

Using ImageJ 1.42q (National Institutes of Health, Bethesda, MD, USA), ROIs were drawn in the lateral and medial SNr and SNc, red nuclei, nucleus dentatus, caudate nucleus, anterior and posterior putamen, anterior and posterior globus pallidus (GP), thalamus, and basilar pons, and, for contrast measurements, the gCC. The ROIs were drawn in a single slice where they were best seen (Figure 2). Their size was adapted to the size of the structure, but the borders of the structures were excluded to avoid partial volume effects. All images were analyzed within 3 weeks by the same person (M.E.R.) to ensure there were similar ROI selections through all patients. Although the first-year images had been analyzed earlier, they were reanalyzed to ensure similar ROI selections for the two time points because intraobserver variability may increase within a 2-year interval.