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BRAIN RESEARCH

Research Report

Characterizing iron deposition in Parkinson's disease using susceptibility-weighted imaging: An in vivo MR study

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ABSTRACT

Brain-iron deposition has been proposed to play an important role in the pathophysiology of Parkinson's disease (PD). The aim of this study was to evaluate the feasibility of characterizing iron deposition in PD using susceptibility-weighted imaging (SWI), and to investigate the correlation of brain-iron accumulation with the clinical status in patients with PD. Forty patients with PD without dementia and 26 age- and sex-matched healthy controls underwent high-resolution susceptibility-weighted magnetic resonance (MR) imaging. The phase shift values of the bilateral red nucleus (RN), substantia nigra (SN), caudate nucleus (CA), globus pallidus (GP), putamen (PU), thalamus (TH) and frontal white matter (FWM) were examined for their relationship with the clinical status. The iron concentrations of the regions involved in PD, such as the SN, increased more significantly, while those in other regions of interest (ROI) did not elevate significantly. No correlation between the increase of the iron concentrations of the SN and duration of PD was observed. PD, however, was closely associated with the Unified Parkinson's Disease Rating Scale motor score (UPDRS-III). No significant differences were found between earlier-onset and later-onset PD patients in terms of the iron concentrations of the SN. Brain-iron concentration can be evaluated by SWI. Also, the brain-iron concentration in the SN correlated with UPDRS motor score, indicating that iron concentration can function as an in vivo biomarker to objectively evaluate the status of PD.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease characterized by loss of dopaminergic neurons, which projects the substantia nigra (SN) and the striatum. The pathogenesis of PD has not yet been fully clarified. Deposition of iron in the brain has been proposed to play an important role in the pathophysiology of this neurodegenerative disease (Dexter et al., 1987,

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Abbreviations: CA, caudate nucleus; FWM, frontal white matter; GP, globus pallidus; PD, Parkinson's disease; PU, putamen; RN, red nucleus; ROI, region of interest; SN, substantia nigra; SWI, susceptibility-weighted imaging; TH, thalamus; UPDRS, Unified Parkinson's Disease Rating Scale

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1991; Chen et al., 1993). Postmortem examinations suggest increased nigral iron content in the Parkinsonian brain. Abnormal deposition of iron in the SN of the midbrain causes lipid peroxidation, lipid oxidative stress and induces the death of dopaminergic neurons, which in turn gives rise to typical symptoms of PD (Dexter et al., 1987, 1990, 1991; Chen et al., 1993; Griffiths and Crossman, 1993). Detection of the concentration of iron in the brain might be a novel biomarker for evaluating the presence and progression of various neurodegenerative diseases. Scientists have paid more attention to multiple in vivo methods to detect brain-iron levels (Bartzokis et al., 1999; Mondino et al., 2002; Atasoy et al., 2004; Sohmiya et al., 2004; Gerlach et al., 2006; Kosta et al., 2006; Michaeli et al., 2007; Martin et al., 2008; Wallis et al., 2008; Sitburana and Ondo, 2009).

Susceptibility-weighted imaging (SWI) has a new type of contrast in MRI. This novel method exploits the magnetic susceptibility differences in various tissues (Ogg et al., 1999; Haacke et al., 2004, 2007a,b; Xu et al., 2008). SWI is a three dimensional gradient echo sequence with full flow compensation and high in-plane resolution. Signals from the substances with susceptibilities different from neighboring tissues can manifest various contrasts. Tissues with different susceptibilities can be differentiated from high-pass filtered SWI phase images. In the past, phase images were seldom used because artifacts from the background field destroyed the integrity of small changes seen in pristine tissue. Phase images contain a wealth of information that may not be observed from the magnitude image. Iron is a paramagnetic element which will strengthen the local magnetic field once in the presence of an external applied magnetic field, that means, the phase of tissues in the presence of changed local magnetic field caused by iron will begin to differ from zero. At a given TE, the more iron content in the tissue, the more the phase differs from zero (positive, in the left-handed system). The contrast seen in a brain image, for example, will depend mainly on how much iron is present. Any changes in the amount of iron will lead to changes in the phase of the tissue relative to its surroundings, which can be used to quantitatively determine the iron concentration of tissue (Haacke et al., 2007a,b).

The emergence of SWI sheds some new light on the in vivo assessment of changes in brain-iron concentration in PD. The purpose of this study is to estimate brain-iron deposition using high-pass filtered phase image of SWI, and to investigate the correlations between brain-iron concentration and clinical status of PD.

2. Results

2.1. Previously published regional iron concentrations vs. our observed SWI phase shift values

In healthy controls, we observed a positive correlation ($r=0.903$, $P=0.005$) between SWI phase shift values and previously published regional iron concentrations as illustrated in Fig. 1 (Hallgren and Sourander, 1958). This validates our application of SWI as a viable MRI method for the noninvasive estimation of regional brain-iron content.

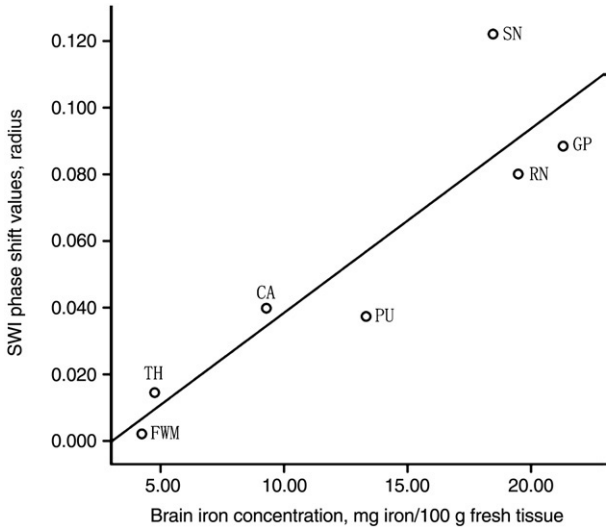

Fig. 1 – Correlation of the phase shift values in seven brain subregions of 26 healthy controls with postmortem brain iron concentrations in the corresponding subregions, as reported by Hallgren and Sourander ($r=0.903$, $P=0.005$).

2.2. Hemispheric differences in the healthy controls

The mean phase shift values in CA, RN, SN, GP, PU, TH and frontal white matter (FWM) in the healthy controls were shown in Table 1. There were no significant hemispheric differences with regards to phase shift values in the healthy human brain (Fig. 2).

2.3. The most affected vs. the least affected brain side in PD

The most affected body side of symptoms is assessed with Unified Parkinson's Disease Rating Scale (UPDRS) motor score. The contralateral brain side is referred as "the most affected brain side"; the ipsilateral brain side referred as "the least affected brain side". The mean phase shift values in CA, RN, SN, GP, PU, TH and FWM in the patients with PD were shown in Table 2. The paired-sample *t*-test showed a difference between the controls and the patients in the SN ($P=0.000$), but not in the other regions studied (Fig. 2).

Table 1 – Hemispheric differences of the phase shift values in healthy controls (mean ± SD).

ROI	Left hemisphere	Right hemisphere	t value	P value
RN	0.08214 ± 0.02729	0.07808 ± 0.02280	1.256	0.221
SN	0.12454 ± 0.04375	0.11959 ± 0.03995	0.793	0.435
CA	0.04075 ± 0.01238	0.03892 ± 0.01260	0.867	0.394
GP	0.09276 ± 0.01231	0.08415 ± 0.05728	1.413	0.170
PU	0.03745 ± 0.02092	0.03733 ± 0.04350	0.016	0.987
TH	0.01403 ± 0.00768	0.01498 ± 0.00638	−0.992	0.331
FWM	0.00200 ± 0.00452	0.00230 ± 0.00526	−0.417	0.680

Note: CA: caudate nucleus, PU: putamen, RN: red nucleus, SN: substantia nigra, GP: globus pallidus, TH: thalamus, FWM: frontal white matter, ROI: region of interest.