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Phase value assessment reveals iron accumulation in parkinson disease

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Abstract

PD is characterized by iron accumulation in the substantia nigra (SN) different from healthy controls. We aim to quantify iron accumulation via susceptibility weighted imaging (SWI) in Parkinson disease (PD). Twenty patients with PD and 21 healthy controls were included in this study. The SWI phase value was evaluated from SN in two areas (middle midbrain and lateral side of middle midbrain) at the axial plane for both sides (right and left). The PD group was divided into two subgroups after clinical examination: the affected side (AS), which was the contralateral of the clinically prominent side and the non-affected side (NAS). The subgroups were analyzed individually. The results of both sides compared between the PD and control groups, as well as between the PD subgroups. The phase values were statistically different in the PD-AS and control group in both areas (< 0.001). Furthermore, at the middle midbrain, the PD-NAS showed a statistical difference compared with the control group (p=0.002). Within the PD groups, only the lateral side of the middle midbrain area (LMMA) demonstrated a statistical difference between the AS and NAS subgroups (p = 0.005). Phase value assessment is useful to demonstrate the effect of iron accumulation on substantia nigra in PD.

Keywords: Parkinson disease, susceptibility weighted imaging, iron accumulation, substantia nigra, phase value

Introduction

Parkinson's disease (PD) is a progressive, neurodegenerative disease, affecting 1–2 per 1,000 of general population at any time, but in daily neuroradiology practice, neuroimaging still offers limited information and is used specifically to exclude Parkinson-plus syndromes [1]. Furthermore, at early-stage of Parkinson-plus syndromes, differential diagnosis of PD with conventional methods present certain difficulties.

PD is characterized by the degeneration of nigrostriatal dopaminergic neurons located at specific areas of substantia nigra (SN) at the midbrain [2]. SN consists of the following two parts: the pars compacta (SNpc) and the pars reticularis. Dopaminergic neurons are located in SNpc, and previous research has demonstrated that especially the ventrolateral area of SNpc is destroyed in PD [3].

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SN neurodegeneration demonstrates asymmetric involvement in PD that begins and predominately affects only one side, but as the disease progresses, the contralateral SN is also involved. As a result of asymmetric involvement tremor arising contralateral to the most affected side. In contrast, the iron amount in the basal ganglia has not been shown to have lateral asymmetry in healthy people [4].

Although the exact mechanism of PD remains unknown, studies have revealed that iron accumulation occurs in PD, like most other neurodegenerative diseases [5,6]. As a result, researchers focused on demonstrating iron accumulation in PD cases to facilitate early diagnosis and predict outcomes in longitudinal follow-ups.

Iron plays an essential role in various biochemical functions, as well as catalyzing lipid peroxidation and free radical formation. The relationship between iron and neurodegeneration is well known, but there is no evidence supporting the idea that iron accumulation is a result or reason of pathologies. Since iron accumulates non-proportional to the aging process in neurodegenerative diseases involving different areas, studies have been undertaken to quantify iron using various methods, such as susceptibility-weighted imaging (SWI).

SWI is a new sequence that uses the differences in susceptibility between tissues, in contrast to the conventional sequence based on spin density [7]. SWI is high-resolution 3D gradient-echo imaging consisting of magnitude, phase and minimum intensity projection (mIP) images. SWI has various areas of use and high pass filtered phase images alone are valuable for quantifying iron [8].

In the current study, we aimed to demonstrate iron accumulation via SWI phase images and correlate it with neurodegeneration.

Materials and Methods

Subjects

Twenty patients with PD and 21 healthy controls were included in this prospective study. The mean age was 67 ± 10.2 years in PD and 64.2 ± 7.8 in the control group. The PD group consisted of six female and 14 male patients, and the control group comprised eight women and 13 men. The control group was recruited from individuals who underwent an MRI scan in our clinic with the complaint of headache. The subjects with abnormal MRI scan results were excluded from the study.

The PD group contained patients with a diagnosis of idiopathic PD based on the UK Parkinson's Disease Society Brain Bank Criteria. The groups were evaluated by a neurologist (E.B.D). Only the right-handed subjects were included in this study. After neurologic examination, all the patients evaluated in terms of the Hoehn and Yahr Scale (H-Y Scale), and those that were found to have stage 4-5 PD were excluded from the study. Furthermore, the individuals with Mini-Mental State Examination scores of below 26 were also excluded from both groups. Other exclusion criteria were history of cardiovascular, metabolic, systemic inflammatory or additional neurologic/psychiatric diseases.

All patients in the PD group were on anti-Parkinsonian medication during examination. The patients' medical history and physical examination results were evaluated to determine the clinically affected, and the contralateral of the clinically affected side was regarded as AS of SN. In the PD group, the left side was clinically affected in nine individuals and the right side in 11 individuals.

All evaluations were performed after obtaining written consent from each subject and approval from the local Ethics Committee, in compliance with the national legislation and the Declaration of Helsinki.

MRI Acquisition

A 3 Tesla MRI system (SKYRA Siemens) with a 16-channel head coil was used for MRI examination. The MRI protocol contained T1-weighted, T2-weighted, fluid-attenuated inversion recovery, diffusion, and SWI sequences. SWI imaging was obtained from the magnitude, phase, SWI, and SWI MIP images with the acquisition parameters of 0.9 mm isotropic resolution with TR 60 TE 30 and 7 minutes 5 seconds duration.

The SWI images were obtained in an axial- oblique orientation parallel to the floor of the fourth ventricle.

Image Processing and Analysis

The raw phase images were loaded to SPIN (SPIN, Magnetic Resonance Innovations Inc., Detroit, MI, USA) software and high pass filtered phase images was performed. The final 64 x 64 high-pass-filtered images were obtained using a phase mask. The phase values were quantified as previously described by Haacke et al. [8]. The phase shift values between -π and + π were converted to 0 to 4096 using SPIN software.

The phase shift values were obtained from the following two areas of SN: middle midbrain (MM) and the lateral side of the middle midbrain (LMM), separately for the right and left sides. The determination of the level of area was undertaken according to the red nucleus. To prevent the possibility of contamination of the iron in the subthalamic nucleus the SN assessment was performed below the inferior half of the red nucleus and the level was adjusted in the coronal section from the 3D image. The MM area was obtained from the inferior half of the red nucleus and the LMM area at the same level but only including the lateral half of SN; i.e., focusing on the lateral-ventral side of SNpc. (Figure 1) The area boundaries were drawn with a freehand region of interest on the magnitude image and pasted on the phase image (Figure 2).

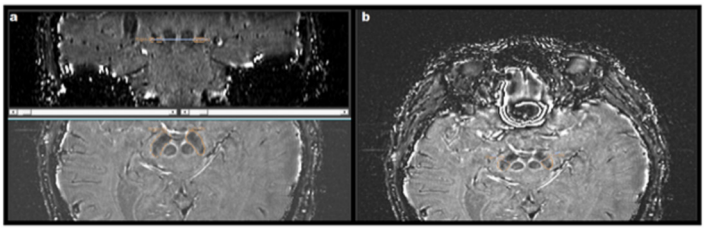

Figure 1. A: The MM area drawing is shown. The level of area checked from coronal wiev. **B:** At the LMM area drawing only lateral half of SN boundary was taken

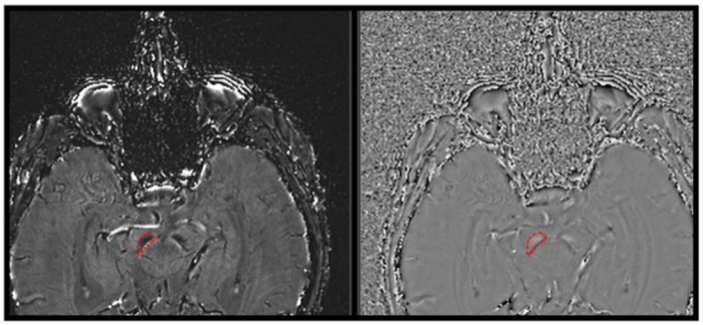

Figure 2. The area boundaries are drawn from magnitude images and then pasted to phase images

Statistical Analysis

The numeric value was noted for each side (right and left) in the control group. The PD group was divided two subgroups as the affected side (AS) and the non-affected side (NAS). The differentiation was made by a neurologist according to the clinically dominant side by regarding the contralateral SN of the clinically dominant side as. The results of the AS and NAS subgroups were noted individually.

In the statistical analysis of the control group phase values, the left and right sides were compared with each other, as well as with the PD subgroups AS and NAS. Furthermore, the AS and NAS subgroups were compared.

The statistical analysis was performed using the ANOVA test (SPSS version 21.0 software), and $p < 0.05$ was considered as statistically different and $p < 0.001$ as significantly different.

Results

The clinical and demographic characteristics of the control and PD groups are presented in Table 1. In the control group, the comparison of the right and left sides did not reveal any significant differences in either area.

Table 1. Demographic characteristics of the control and PD groups

	NUMBER	AGE	H-Y SCALE
PD GROUP	20	67 ± 10.2	median 2 (1-3)
CONTROL GROUP	21	64.2 ± 7.8	

H-Y Scale: Hoehn and Yahr Scale

When the control group was compared with the PD subgroups for two levels individually, the MM and LMM phase values were significantly higher in PD-AS ($p < 0.001$), and the MM phase value was statistically higher in PD-NAS compared ($p = 0.002$). Furthermore, the PD subgroups (AS and NAS) significantly differed only in terms of LMM results ($p = 0.005$). Results and statistical analysis are shown in Table 2.

Table 2. Results and statistical analysis of the control and PD groups

	Middle midbrain	Lateral side of Middle midbrain
Control group	2043	2043
Parkinson Efected	2061	2069
Parkinson Nonefected	2064	2035
Control&PD Efected	< 0.001	< 0.001
Control&PD Non-Efected	.002	.162
PD Efected& PD Non-Efected	1.000	.005

*The mean difference is significant at the 0.05 level.

Discussion

In this prospective study, we assessed the phase values obtained from SWI to determine whether iron accumulation was correlated with neurodegeneration of SN in early stages of PD. The phase values for the MM and LMM areas were found to be higher in the PD-AS subgroup compared with the control group, which confirms the results reported by Wallis et al., who used the T2 relaxation rate to demonstrate iron accumulation [9]. Additionally Bastida et al. who used to phase value similarly our study showed SN depicted statistical significant difference at comparation of most affected and least affected side [10].

Additionally, the PD-AS subgroup demonstrated a higher phase value at MM compared with the control group. When the phase values of the AS and NAS subgroups were compared in terms of the LMM area, a statistical difference was observed. This result provides evidence that neurodegeneration develops and continues predominantly on one side, but after a while, it begins to affect the opposite side.

It is known that specific areas of the human brain, such as SN and the globus pallidus physiologically contain a high amount of iron, and iron accumulation increases with the aging process. However, research has also shown that abnormal iron accumulation increases disproportional to aging in various neurodegenerative diseases. Recently, various studies have been undertaken to investigate iron accumulation in different areas of the brain in patients with different conditions using different methods.

Concerning PD, some researchers focused on quantifying the neuromelanin amount in SNpc. A large part of neuromelanin is produced in dopaminergic neurons and plays an important role in iron chelation [11]. The results of imaging studies conducted with PD patients reveal that the amount of neuromelanin decreases, but the amount of iron in SNpc increases [12-14]. Nigral degeneration occurs especially at the lateral ventral tier of SNpc [15]. Furthermore, recent research on iron imaging focuses on depicting healthy nigrosome 1 that includes dopamine-containing neurons and is important since in PD cases it demonstrate highest rate of neurodegeneration with 98% [15]. Schward et al. identified nigrosome 1 at the SWI sequence and determined its diagnostic accuracy in PD and healthy subjects. In healthy subjects, nigrosome 1 was seen as a hyperintense, wedge-shaped area preserved from iron accumulation on the iron-rich lateral ventral tier of SNpc [16]. These findings were also supported by following studies [17,18]. In the current study, we evaluated the midbrain in two parts and focused on the nigrosome 1 location at the lateral part of SNpc. In our comparison of the PD subgroups, we found more iron accumulation in AS compared to NAS for the LMM area. This finding is important because we claim that the LMM area corresponds to the location of nigrosome 1 and quantified methods might overcome problems related to individual factors, such as the radiologist's experience. Our results, demonstrating asymmetry, are consistent with those of Zhang et al. and Bastida et al. who showed the phase shift value with SWI, and Azuma et al., who evaluated the mean susceptibility value using QSM [10,19,20].

There wasn't any difference between right and left sides in control group. This result is consistent with a previous study that demonstrated that handedness was not associated with asymmetric phase value [21].

This study has certain limitations. First, although we investigated the early pathologic changes on SNpc, six patients in the PD group were stage 3 according to the H-Y scale classification. SNpc involvement tends to be bilateral at the advanced stage of

PD, which might have affected our results because we aimed to find unilaterality of neurodegeneration, prominent at early stages of the disease. Second, our study included only a limited number of subjects and we did not evaluate patients with Parkinson-plus syndromes. In future studies, determination of the differences in the pathological changes between idiopathic PD and Parkinson-plus syndromes could help diagnosis in difficult cases.

Conclusion

In conclusion we determine asymmetric involvement of SNpc in PD with SWI phase value. SWI phase value assessment was evaluated by windows based easily applicable software. In future studies, determination of the differences in the pathological changes between idiopathic PD and Parkinson-plus syndromes could help diagnosis in difficult cases.

Conflict of interests
The authors declare that they have no conflict of interest.

Financial Disclosure
All authors declare no financial support.

Ethical approval
All evaluations were performed after approval from the local Ethics Committee, in compliance with the national legislation and the 1964 Declaration of Helsinki and its later amendments.

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