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Evaluation of Substantia Nigra Volume of Patients with Parkinson's Disease Using 3-dimensional Neuromelanin Images

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Abstract

Objective: The purpose of this study was to evaluate the volume of the substantia nigra of patients with Parkinson's disease using 3-dimensional neuromelanin imaging, and to investigate the relationship between substantia nigra volume and movement disorders.

Methods: The substantia nigra volume found in 26 patients with Parkinson's disease (11 males, 15 females) was compared to that in 27 healthy participants (12 males, 15 females). In addition, the PD group was stratified into a "serious" group (Hoehn and Yahr scale III, IV, V) and a "mild" group (Hoehn and Yahr scale I, II). Three-dimensional neuromelanin images were acquired on a 3.0 Tesla MRI system, and the data were analyzed using ImageJ free software. The relationship between the Hoehn and Yahr scale and substantia nigra volumes in patients was also evaluated.

Results: The volume of the substantia nigra in the group with PD was significantly lower than that in the healthy group; moreover, in the PD group, the signal strength of the substantia nigra appeared weakened at its outer regions. Volumes were significantly lower in patients than in healthy participants. However, there was no significant difference in substantia nigra volumes between "serious" and "mild" patient subgroups within the patient group.

Conclusion: This study shows that the degeneration of the substantia nigra in patients with Parkinson's disease can be evaluated by 3-dimensional neuromelanin imaging. Three-dimensional neuromelanin images exhibited small slice thickness and no slice gap, suggesting that this method can be used to evaluate substantia nigra volume more accurately compared with two-dimensional neuromelanin imaging. However, the results suggest that secondary impairments affect the severity of motor impairments in addition to the degeneration of the substantia nigra, and therefore provide evidence for rehabilitation programs that can prevent or improve such secondary impairments.

Keywords: Substantia nigra; Parkinson's disease; Neuromelanin; Movement disorders; Hoehn and Yahr scale; Motor impairment; 3-dimensional imaging

Introduction

Parkinson's disease (PD) is a chronic progressive neurodegenerative disease caused by denaturation and detachment of dopamine neurons in the substantia nigra (SN) of the midbrain; rehabilitation from PD requires an exercise program that is adapted to the severity of the patient's motor symptoms. However, the execution of activities of daily living (ADL) of patients with PD is made difficult by motor symptoms (tremor, muscle rigidity, bradykinesia, and postural instability) and secondary impairments such as a decrease in the overall amount of activity [1]. Therefore, in order to accumulate the available evidence for rehabilitation programs, we think that it is necessary to consider the severity of the patient's movement disorder in relation to the degree of degeneration of their SN.

Although it has been considered difficult to evaluate the degeneration of the SN on magnetic resonance imaging (MRI), in recent years, a method for capturing melanin contained in dopamine cells of the SN (neuromelanin imaging, NMI) has been developed. Tanaka et al. [2] and Sasaki et al. [3] evaluated the signal intensity of the SN of patients with PD using NMI, and reported that patients with PD had lower signal intensity than healthy individuals and that the number of pixels of the SN was different depending on the severity of symptoms according to the Hoehn and Yahr (HY) scale. However, since the NMI technique used in previous studies acquired only 2 dimensions, the spatial resolution of these evaluations was low, and the total volume of the SN might not have been correctly evaluated.

In this study, we measured the volume of the SN using NMI in 3 dimensions without slice gap, and compared the volumes found in patients to those in healthy participants. In addition, we investigated the relationship between the HY scale and the volume of the SN in patients with PD.

Subjects and Methods

The subjects were 26 patients with PD who underwent NMI at Fukuoka Sanno Hospital (11 males, 15 females, 67.5 ± 7.9 years old) and 27 healthy participants (12 males, 15 females, 75.9 ± 7.6 years old). The ethics review board of our college and hospital approved this study (No.14-Ig-01, No.FS-95), and we obtained informed consent from all subjects.

Cases of PD were diagnosed by doctors, and the patients had no history of stroke or head trauma. Healthy participants showed no abnormal signals on head MRI images, had scores higher than 20 on the revised version of the Hasegawa's Dementia Scale (HDS-R), and a negative diagnosis of dementia.

NMI images were acquired on a 3.0 Tesla MRI system (PHLIPS Achieva 3T) using fast field echo, with the following parameters: fast field echo matrix size: 320 × 242FOV: 200 × 200 mm^2slice thickness: 1 mm, voxel size: 0.35 × 0.35 × 1 mm^3, TR: 27 ms, TE: 5.7 ms, flip angle: 20°. The total imaging time was less than 7 min. We used the free software Image J [4] to analyze the NMI data.

First, all NMIs were converted to 8 bits and smoothed by an averaging filter (3×3). Subsequently, NM images were binarized using the threshold value at which the high contrast of the SN and the periaqueductal grey became clear, as described in a previous study (Figure 1) [2]. Thereafter, the number of pixels of the SN was calculated on both sides for all slices and converted into volumes (SN-vol). Furthermore, the HY stage of all patients with PD was examined by a physiotherapist. Finally, the SN-vol was compared between the PD group and the healthy group using the Mann-Whitney U test.

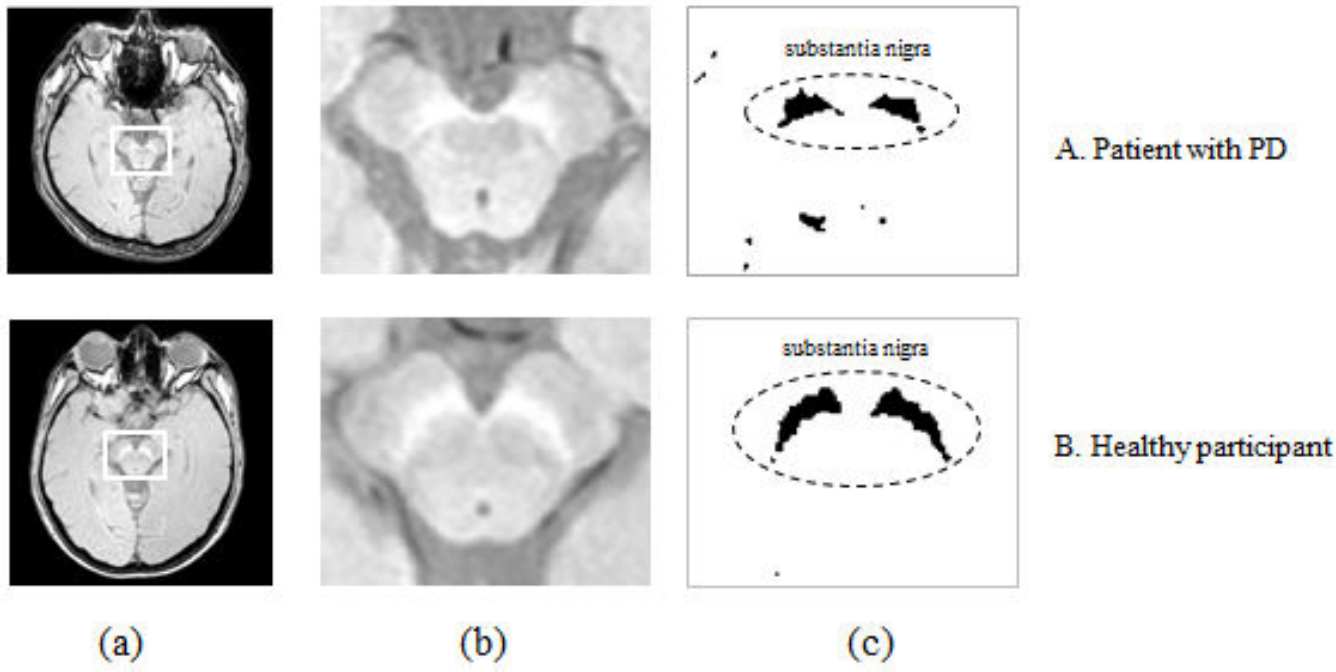

Figure 1: Process of convert Neuromelanin image into binary image ((a) Neuromelanin image, b) converted to 8 bits and smoothed, c) binarized using the threshold)).

In addition, the PD group was classified into a "serious" group (HY stages III, IV, V) and a "mild" group (HY stages I, II), and the SN-vol of both groups were compared using the Mann-Whitney U test. We used SPSS for Windows for statistical analyses, and a significance level of $p<0.05$.

Results

SN-vol was 136.60 ± 75.14 mm^3 in the PD group and 238.93 ± 71.09 mm^3 in the healthy group, and the SN-vol of the PD group was significantly lower than that of the healthy group ($p<0.001$) (Table 1).

	Patients with PD (n=26)	Healthy participants (n=27)	Significance
Age (mean; SD years)	67.5 ± 7.9	75.9 ± 7.6	
Gender	11 M/15 F	12 M/15 F	
volume of SN (mean; SD mm^3)	136.60 ± 75.14	238.93 ± 71.09	p<0.001†

Table 1: Demographic and volume of substantia nigra in patients with PD and healthy participants (†Mann-Whitney U test).

In addition, in the PD group, signal intensity weakening was observed in the outer part rather than the inner part of the SN. The HY stages found in the PD group were as follows: stage I (4 participants), stage II (3), stage III (12), stage IV (7), stage V (0). The SN-vol of each HY stage were the following: stage I: 125.52 ± 39.91 mm3, stage II: 200.47 ± 91.42 mm^3, stage III: 111.62 ± 66.89 mm^3, stage IV: 158.40 ± 73.81 mm^3. There was no significant difference in SN-vol between the serious and mild groups within the PD group (Table 2).

	Mild group (HY stages I, II)	Serious group (HY stages III, IV)	Significance
Age (mean; SD years)	65.6 ± 9.1	68.2 ± 7.1	
Gender	6 M/1 F	5 M/14 F	
Volume of SN (mean; SD mm^3)	157.64 ± 76.60	128.85 ± 73.09	n.s.†

Table 2: Demographic and volume of substantia nigra in Mild group and serious group († Mann-Whitney U test, n.s: not significant).

Discussion

Neuromelanin is produced by the dopamine metabolism in the SN of the midbrain [5]. Neuromelanin shortens the T1 signal by combining with iron and copper, and thus leads to the appearance of high signal regions on NMI [3]. Therefore, since the pathology of PD includes the denaturation of dopamine neurons in the SN, PD signal intensity of the SN has been found to decrease on NMI [2,3].

In this study, the volume of the SN of a group with PD was significantly lower than that of a healthy group, and the signal strength of the SN in the PD group appeared weakened at the outer part. Pathological studies have reported that denaturation of the SN in PD begins at the outer part and then proceeds towards the central part [6]. The results of this study are therefore in line with pathological studies of PD, and they show that the degeneration of the SN in PD can be evaluated using 3D NMI.

In contrast, there was no significant difference in the volume of the SN between the severe group and the mild group within the PD group.

Tanaka et al. [2] calculated the number of pixels in the SN using 2D NMI, and reported that the number of pixels depends on the severity of the patient's motor symptoms. However, 2D NMI is susceptible to partial volume effects, due to the large slice thickness, and it is thus possible that SN volumes might not have been calculated correctly because of the influence of the slice gap.

To analyze the degeneration of the SN in detail, 3D NMI as used in this study is thus more suitable than the 2D NMI approach with slice gap used in previous studies, and the relationship between the severity of movement disorder and the denaturation of the SN revealed here should therefore be more accurate. In addition, Gattellaro et al. [7] reported microstructural damage in the corpus callosum and superior longitudinal fasciculus of patients with PD on diffusion tensor imaging. This suggests that, in addition to the denaturation of the SN, secondary factors affect the HY stage.

A limitation of this study is that we did not consider the relationship between SN volume and disease duration, since PD has no clear onset date. In addition, further data should be gathered to clearly evaluate the difference between the PD groups with mild and severe motor symptoms. It will therefore be necessary to investigate the relationship between changes in SN volumes of more subjects and difficulties in ADL in longitudinal studies in the future. For that purpose, we think that it would be useful to evaluate the volume of the SN using 3D NMI.

In conclusion, this study showed that the causes of motor impairment in PD, in addition to the denaturation of the SN, are problems caused by inactivity, such as weakening of muscle strength, as well as microstructural white matter damage and a reduction in the range of joint motions. Because PD is a chronic progressive disease, it is generally assumed that rehabilitation has no effect on SN degeneration. However, secondary impairments can be prevented or improved by rehabilitation. Therefore, in order to obtain evidence regarding the effectiveness of the PD rehabilitation program, it may be necessary to calculate the SN volume using 3D NMI and investigate the relationship between severity of movement disorder and daily exercise time.

Conflict of Interest

The authors declare no conflicts of interest.

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