Reduction of Neuromelanin-Positive Nigral Volume in Patients with MSA, PSP and CBD

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Abstract

Objective Diseases presenting extrapyramidal symptoms are accompanied by nigral cell loss. In the previous study, we demonstrated the reduction of the neuromelanin-positive volume of substantia nigra (SN) pars compacta (SNc) in patients with Parkinson’s disease (PD) using 3-Tesla MRI. In the present study we investigated the neuromelanin-positive SNc volume in patients with the other parkinsonian disorders including multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) and compared the results with those with PD, spinocerebellar ataxia (SCA) and controls.

Patients and Methods Axial T1-weighted (T1W) images were obtained with a 3-Tesla MRI scanner. The border of the neuromelanin-positive region of the SNc was traced manually on these images with a pentablet pointing device and the SNc volume was calculated. The SNc volumes of 28 patients with MSA, 11 patients with PSP and 10 patients with CBD were compared with those of 80 patients with PD, 9 patients with SCA and 54 patients who had suffered mild acute ischemic stroke as controls. The mean volumes for the left and right SN were used for statistical analyses.

Results The volumes of the neuromelanin-positive SNc region in patients with MSA, PSP and CBD, but not SCA were reduced to the same extent as PD patients compared with controls.

Conclusion Reduced volume of the neuromelanin-positive SNc region of patients with MSA, PSP and CBD was detected by neuromelanin MR imaging. Volumetric evaluation of neuromelanin MR imaging may provide a biomarker of nigral degeneration in patients with MSA, PSP and CBD as in patients with PD.

Key words: substantia nigra, neuromelanin, MRI, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration


Introduction

Multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are disorders that exhibit extrapyramidal symptoms. The pathology of these disorders shows progressive nigral cell loss similar to Parkinson’s disease (PD) (1-4). Sasaki et al reported that T1-weighted (T1W) imaging of 3-Tesla MR imaging detects neuromelanin in the substantia nigra (SN) pars compacta (SNc) in vivo (5, 6). In a previous study, we demonstrated neuromelanin-positive SNc volume loss in patients with PD depending on disease severity and duration (7). In the present study, we determined the neuromelanin-positive SNc volume in patients with MSA, PSP and CBD and compared the results with those of patients with PD, spinocerebellar ataxia (SCA) and controls.

Patients and Methods

Patients

We examined 28 patients with MSA (11 men, 17 women), 11 patients with PS (8, 3), 10 patients with CBD (4, 6), and 9 patients with SCA (5, 4) who visited our hospital and underwent MR imaging between June 1, 2008 and

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April 30, 2010. Diagnoses of probable MSA, PSP, CBD and PD were made according to the consensus criteria for each disease (8-11). SCA was diagnosed when patients exhibited progressive ataxia accompanied by cerebellar atrophy on MR images without any clinical or radiological abnormality of any other nervous system part. This study was approved by the Ethics Committee of Okayama Kyokuto Hospital. Informed consent was obtained from each patient prior to the study.

**MRI Data acquisition**

All MR images were obtained with a 3-Tesla MRI scanner (Signa HD, GE Healthcare, Milwaukee, WI, USA). That is, the pulse sequence used to acquire axial T1W images was T1W fast spin echo; 600/10 (repetition time/effective echo time), two echo train length, 15 slices, slice thickness 2.5 mm with 1-mm intersection gaps, matrix size 512×320, field of view 220 mm (pixel size: 0.43×0.69 mm) and acquisition time 6 minutes 27 seconds. The sections were in the oblique axial direction perpendicular to the fourth ventricle floor. Area coverage extended from the splenium of the corpus callosum to the inferior border of the pons. We also obtained axial T2-weighted images, T2*-weighted images, fluid-attenuated inversion recovery images (FLAIR), diffusion-weighted images and sagittal FLAIR images of the entire brain for the differential diagnosis of PD, MSA, PSP, CBD and SCA.

**Volumetric measurements**

The border of the SNc neuromelanin-positive region was traced manually on the axial T1W images, starting in the most posterior slice in which any SNc neuromelanin-positive region could be observed, using a pentablet pointing device. The left and right SNcs of subjects were each measured twice in random order by skilled raters (TS and FH) who were blind to the subjects’ identity and classification. The mean volumes of SNcs were then calculated as described previously (7). Inter-rater agreement of the measurements was confirmed in the previous study (7).

**Statistical analysis**

Differences in age, disease duration and the volume of the neuromelanin-positive SNc volume for the controls and patients with each of the parkinsonian disorders were analyzed by a one-way analysis of variance (ANOVA) test and Bonferroni’s test post hoc. p<0.05 was considered significant in all of the analyses.

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\text{Table 1. Data for Control Patients and Patients with PD, MSA, PSP, CBD and SCA}\\
\begin{array}{cccccc}
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& \text{Controls} & \text{PD} & \text{MSA} & \text{PSP} & \text{CBD} & \text{SCA} \\
\hline
\text{n} & 54 & 80 & 28 & 11 & 10 & 9 \\
\text{(M, F)} & (28, 26) & (35, 45) & (11, 17) & (8, 3) & (4, 6) & (5, 4) \\
\text{Age} & 71.6 & 70.9 & 68.5 & 74.5 & 70.7 & 67.8 \\
& (mean years ± SD) & ±10.8 & ±8.2 & ±9.0 & ±4.6 & ±10.7 & ±9.6 \\
\text{Disease Duration} & 5.1 & 3.9 & 3.4 & 4.1 & 4.2 \\
& (mean years ± SD) & ±4.7 & ±2.0 & ±2.8 & ±4.2 & ±4.7 \\
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\end{array}
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There is no age difference between the controls and patients with PD, MSA, PSP, CBD and SCA (p = 0.429).

There is no difference in the disease duration of patients with PD, MSA, PSP, CBD and SCA (p = 0.479).

**Results**

Patients’ characteristics are given in Table 1. Mean age ± SD was 71.6±10.8 years for the controls, 70.9±8.2 years for the patients with PD, 68.5±9.0 years for MSA, 74.5±4.6 years for PSP, 70.7±10.7 years for CBD and 67.8±9.6 years for SCA. The ANOVA test revealed no age difference among these groups (p=0.429). The mean disease duration ± SD was 5.1±4.7 years for those with PD, 3.9±2.0 years for MSA, 3.9±2.8 years for PSP, 4.1±4.2 years for CBD and 4.2±2.7 years for SCA. The ANOVA test revealed no difference of disease duration among these groups (p=0.479). A representative neuromelanin MR image of a patient with each disease is shown in Fig. 1. Control subjects and patients with SCA showed high signal intensity in the SNc bilaterally, whereas the intensity was reduced and the high-signal region was diminished in patients with MSA, PSP and CBD as well as in PD. The calculated mean volume ± SD of the neuromelanin-positive SNc region for controls was 128.4±35.7 mm³, 96.9±38.2 for PD, 90.7±45.5 for MSA, 72.5±43.2 for PSP, 84.7±53.5 for CBD and 126.6±32.6 for SCA (Fig. 2). The ANOVA and Bonferroni post hoc tests showed significantly lower neuromelanin-positive SNc volumes in patients with MSA (p<0.001), PSP (p<0.001) and CBD (p<0.001) as well as those for PD (Fig. 2) compared to controls. Neuromelanin-positive SNc volume in the patients with SCA was not decreased when compared with the mean volume from controls (p=0.895) (Fig. 2).

**Discussion**

Patients with MSA (2), PSP (3) and CBD (4) are known to show nigral cell loss, similar to patients with PD (1). To date, the evaluation of central nervous system abnormalities in living patients with extrapyramidal symptoms was performed using MR imaging and/or functional imaging such as positron emission tomography (PET) and single photon...
emission topography (SPECT) (12). Brain MR imaging is a non-invasive, rapid and relatively inexpensive measure for evaluating changes in anatomy, tissue characteristics and neuronal fiber tracts. Reported anatomical changes on MR images appear to be characteristic to each extrapyramidal disorder, including midbrain atrophy in patients with PSP, pons and cerebellar atrophy in patients with MSA and asymmetric cerebral cortical atrophy in patients with CBD (13). As tissue characteristics change, putaminal rim hyperintensity on T2-weighted MR images may have diagnostic value in patients with MSA (13). These diseases usually show extrapyramidal symptoms in association with nigral cell loss (2-4). In patients with PD, neuromelanin-containing nigral cell loss develops as the disease progresses (1). However, MR imaging techniques have failed to detect such SNc degeneration in vivo. Post-mortem studies of patients with PD have shown increased iron accumulations (14, 15) and reduced neuromelanin concentrations (16) in the SNc. Iron imaging by quantitative T2 measurement has shown increased regional iron content in the SNc (17-20). Several authors reported increased putaminal apparent diffusion coefficient in patients with MSA (21, 22) and PSP (23) and increased diffusivity in patients with MSA (24).

Recently Menke et al (25) delineated the volume of SN by means of MR imaging with high-resolution mapping
technique and revealed smaller volumes of the SN in patients with PD. Sasaki et al (5) determined neuromelanin imaging signal intensity using 3-Tesla MR imaging and found the great reduction of the intensity in the locus ceruleus and SNc of PD patients. In the previous report we assessed the volume of the neuromelanin-positive SNc region on 3-Tesla MR images (7). The SNc volume in PD patients decreased significantly, and the amount of decrease was related to disease severity and duration (7). In the present study, we found a similar reduction of neuromelanin-positive SNc volume in patients with MSA, PSP and CBD but not in those with SCA. In SCA patients, the cerebellum but not SN may be involved in the degeneration. Our findings indicate the apparent volume loss of the neuromelanin-positive SNc region in patients with MSA, PSP and CBD as well as those in PD. The volume loss is most marked in PSP patients followed by MSA and CBD patients, although differences were not statistically significant (Fig. 2). Not only rapid progression of neurodegenerative change of the SNc but also atrophy of midbrain in patients with PSP may explain the marked volume loss in PSP.

The present results show that degeneration of the SNc in patients with MSA, PSP and CBD, as well as PD, may be detected by MR imaging with 3-Tesla scanning. This technique, however, may not be able to differentiate these diseases. Reduction of neuromelanin-positive SNc volume may be used as a biomarker to detect PD, MSA, PSP and CBD from other diseases presenting extrapyramidal symptoms or cerebellar signs including idiopathic normal pressure hydrocephalus, vascular parkinsonism and drug-induced parkinsonism.

Our study has limitations. Diagnosis of each disease has not been confirmed with histopathology. There was a considerable overlap between the SNc volumes of the controls and patients with MSA, PSP, CBD and PD. Despite the above limitations, our findings clearly show that nigral cell loss in living patients with extrapyramidal symptoms can be detected by MR imaging using 3-Tesla scanning.

**Conclusion**

Since neuromelanin imaging can show decreases in neuromelanin content, it may indicate loss of neuromelanin-containing neurons in the SNc of patients with MSA, PSP, CBD and PD. Volumetric evaluation of the neuromelanin-positive SNc region may detect specific characteristics of diseases presenting extrapyramidal symptoms that involve the SNc.

The authors state that they have no Conflict of Interest (COI).

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