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Changes in substantia nigra and locus coeruleus in patients with early-stage Parkinson's disease using neuromelanin-sensitive MR imaging

Chigumi Ohtsuka[a,*], Makoto Sasaki[b], Kanako Konno[a], Mizuho Koide[a], Kanako Kato[a], Junko Takahashi[a], Satoshi Takahashi[a], Kohsuke Kudo[b], Fumio Yamashita[b], Yasuo Terayama[a]

[a] Department of Neurology and Gerontology, Iwate Medical University, 19-1 Uchimaru, Morioka 020-8505, Japan
[b] Institute for Biomedical Sciences, Iwate Medical University, 19-1 Uchimaru, Morioka 020-8505, Japan

HIGHLIGHTS

- Neuromelanin MRI can visualize neuromelanin-containing nuclei.
- We investigated the diagnostic accuracy of this technique in the early stages of PD.
- We detected remarkable signal attenuations in the SNc and LC in early PD.
- Neuromelanin MRI can readily distinguish early PD from healthy control.

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ABSTRACT

Neuromelanin-sensitive magnetic resonance imaging is able to visualize changes associated with neuronal loss in the substantia nigra pars compacta (SNc) and locus coeruleus (LC) in patients with Parkinson's disease (PD). However, the diagnostic accuracy of this technique in the early stages of PD remains unknown. Therefore, changes in the SNc and LC observed using neuromelanin imaging were evaluated in patients with early PD. The signal intensities of the lateral, central, and medial parts of the SNc and that of the LC were measured, and the contrast ratios (CRs) were calculated against the adjacent white matter structures. CRs in the lateral part of the SNc and in the LC were significantly reduced in the early PD group when compared with the controls. Sensitivities and specificities in discriminating early PD patients from healthy controls were 73% and 87% in lateral SNc and 82% and 90% in LC, respectively. Neuromelanin imaging can depict signal alterations in the lateral part of the SNc and in the LC in patients with PD, even in its early stage, and can discriminate between these patients and healthy individuals with high sensitivities and specificities.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by neuronal loss in the substantia nigra pars compacta (SNc) and locus coeruleus (LC) and the appearance of Lewy bodies in the remaining neurons in these regions. The decrease in the dopamine content of the corpus striatum resulting from degeneration of the SNc causes dysfunction of the motor control system comprising the basal ganglia, while decreases in the norepinephrine content in the frontal cortices, hypothalamus, and other regions are the result of degeneration of the LC, causing motor symptoms such as frozen gait, autonomic nerve symptoms, and other symptoms such as depression and sleeping disorders [5,9,12].

Although pathological changes in PD have been thoroughly investigated, neuroimaging techniques, e.g. conventional magnetic resonance (MR) imaging, have failed to detect changes that correspond to pathological findings, primarily because of difficulties in the direct depiction of the SNc and LC [3,7,13]. Recently, a neuromelanin-sensitive MR imaging technique at 3 Tesla (3-T) was reported to visualize these neuromelanin-containing nuclei, i.e., the SNc and LC, as distinct high-intensity areas owing to T1-shortening effects of neuromelanin, as well as T1 prolongation and strengthened magnetization transfer effects at 3-T [15,16]. This technique has also been reported to show signal attenuation in the SNc and LC in PD patients when compared with healthy individuals, suggesting the depletion of neuromelanin-containing neurons [16], and to detect signal changes in psychiatric disorders,

* Corresponding author. Tel.: +81 19 651 5111; fax: +81 19 654 9860.
E-mail addresses: csato@iwate-med.ac.jp (C. Ohtsuka), masasaki@iwate-med.ac.jp (M. Sasaki), kkonno@iwate-med.ac.jp (K. Konno), narazaki@iwate-med.ac.jp (M. Koide), kakato@iwate-med.ac.jp (K. Kato), jtakahas@iwate-med.ac.jp (J. Takahashi), stakahas@iwate-med.ac.jp (S. Takahashi), kokudo@iwate-med.ac.jp (K. Kudo), fyamashi@iwate-med.ac.jp (F. Yamashita), teray@iwate-med.ac.jp (Y. Terayama).

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suggesting changes in the intraneuronal neuromelanin content [19,20]. However, it remains unknown whether signal changes in the SNc and LC in neuromelanin-sensitive MR images can occur during the early stages of PD. Therefore, we investigated the findings in the SNc and LC on neuromelanin MR images in untreated PD patients at an early stage.

2. Materials and methods

2.1. Subjects

From November 2006 to December 2010, we prospectively examined 37 consecutive patients with suspected early stage PD. They fulfilled the following criteria: had not received any medical or surgical treatment for parkinsonism and were at Hoehn & Yahr (H&Y) stage 1–2. After an observation period of 1 year, 35 of 37 patients who met the criteria for probable PD (according to the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria for PD [6]) were included in the group of early PD patients. Moreover, 31 consecutive patients with advanced PD having a H&Y stage of 3–5, who were hospitalized for deep brain stimulation or medication adjustment, and 22 age-matched healthy subjects without movement disorder or other neurological disorders were also examined as disease control group and healthy control group, respectively. Unified Parkinson's Disease Rating Scale score (UPDRS) as well as early and late heart-to-mediastinum (H/M) ratios of ^{123}I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy were examined within 2 weeks of MR scan in the PD groups. The evaluation of symptoms of patients with wearing-off was performed at the off state.

We performed all examinations after obtaining approval from the institutional review board and written informed consent from each subject.

2.2. Imaging protocol

Using a 3-T MR scanner (Signa Excite HDxt; GE Healthcare, Milwaukee, WI), we obtained oblique-axial fast spin-echo T1-weighted images (repetition time, 600 ms; echo time, 14 ms; flip angle, 90°; echo train length, 2; number of excitations, 8; matrix size, 512 × 320; field of view, 220 mm; pixel size, 0.42 mm × 0.68 mm; number of slices, 10; slice thickness, 2.5 mm; interslice gap, 1 mm; and acquisition time, 12 min), as described previously [16,17]. These images were carefully set perpendicular to the fourth ventricle floor with coverage between the posterior commissure and the inferior border of the pons. T1- and T2-weighted images of the entire brain were also obtained in all subjects to exclude other neurological disorders, as well as to confirm the absence of coexisting lesions that would interfere with further assessment, such as distinct cerebral infarcts and hemorrhages.

2.3. Data processing and statistical analyses

For quantitative evaluation of the neuromelanin-sensitive MR images, the regions of interests (ROIs) were measured on a liquid crystal display using circular cursors at the following locations: the lateral, central, and medial parts of the bilateral SNc, and the decussation of the superior cerebellar peduncle (SCP) at the section through the lower midbrain, as well as the bilateral LC and the pontine tegmentum (PT) at the section through the upper pons, on which the LC signal was most evident (Fig. 1). One of the authors (K.K.), who was blinded to subject information, performed manual measurements twice with ROIs of 10, 30, 1, and 10 mm^2 for the SNc, SCP, LC, and PT, respectively; the obtained values were then averaged. Contrast ratios (CRs) of the medial, central, and lateral parts of the SNc, as well as of the LC, were calculated using the following equations:

$$\frac{SI_{SNc} - SI_{SCP}}{SI_{SCP}}$$

and

$$\frac{SI_{LC} - SI_{PT}}{SI_{PT}}$$

where SI_{SNc} and SI_{LC} are the averaged values of the signal intensities of the bilateral SNc (medial, central, or lateral parts) and the bilateral LC, respectively, SI_{SCP} is the signal intensity of the SCP decussation and SI_{PT} is the signal intensity of the PT.

For statistical analyses, the Kruskal–Wallis test and post hoc Mann–Whitney *U*-test were used to determine differences in CRs of SNc and LC among the patients with early PD, those with advanced PD, and healthy subjects. These tests were also used to evaluate differences in the clinical characteristics among these groups. To determine the sensitivity and specificity of the neuromelanin-sensitive MR images for discriminating patients with early or advanced PD from healthy subjects, receiver operating characteristic (ROC) analyses were performed. Cut-off values for MR images were determined using the Youden index. Multivariate regression analysis was used to examine whether clinical characteristics were independently related to CRs of SNc and LC. Intra-observer agreement of the measurements was determined by calculating the intraclass correlation coefficient (ICC). The alpha level for all analyses was 0.05.

3. Results

MR imaging was performed on all subjects. However, the quality of the MR images in 5 patients with early PD was suboptimal because of strong motion artifacts. Therefore, 30 patients with early PD, 31 patients with advanced PD, and 22 healthy subjects were eligible for further quantitative analyses. The clinical characteristics of these subjects are shown in Table 1. Among these, only the age was independently correlated with CR of LC ($p = 0.006$, multivariate regression analysis). No significant differences were present in age and sex among the 3 groups, whereas significant differences were present in disease duration, age at onset, H&Y stage, UPDRS score, and H/M ratios between the groups with early and advanced PD. ICC values for the manual measurement of the ROIs were 0.89–0.94, indicating high intra-operator agreement.

The CRs in the lateral part of the SNc were 0.6–9.9% (median, 5.5%), 1.9–12.2% (5.2%), and 4.3–22.4% (10.0%) in the early PD group, advanced PD group, and healthy control group, respectively (Fig. 2A). Among these, CR was markedly decreased in the early and advanced PD groups when compared with the healthy control group ($p < 0.0001$, Kruskal–Wallis test; $p < 0.0001$, post hoc Mann–Whitney *U*-test), whereas no significant difference was observed between the early and advanced groups ($p = 0.86$, Mann–Whitney *U*-test) (Fig. 1A–C). The CRs in the central part of the SNc showed similar tendencies: 6.5–24.3% (median, 14.1%), 6.2–21.1% (12.6%), and 11.1–32.0% (15.6%) in the early PD group, advanced PD group, and healthy control group, respectively ($p < 0.01$, Kruskal–Wallis test). However, substantial overlaps were observed between the early or advanced PD groups and the control group ($p < 0.05$ and $p < 0.005$, post hoc Mann–Whitney *U*-test) (Fig. 2B). No significant difference was observed between the early and advanced groups ($p = 0.42$, Mann–Whitney *U*-test), although the median of CRs of the former tended to be higher than that of the latter. The CRs in the medial part of the SNc showed no significant differences among the 3 groups, although the median of CRs of the advanced PD group tended to be lower than that of the other groups: 5.7–28.5% (median, 19.2%),