Evaluation of Parkinson's disease and Alzheimer's disease using neuromelanin magnetic resonance imaging and $^{123}$I-metaiodobenzylguanidine scintigraphy

Poster No.: C-1200  
Congress: ECR 2013  
Type: Scientific Exhibit  
Authors: F. Miyoshi, S. Kitao, M. Takasugi, Y. Shinohara, Y. Kanasaki, S. Fujii, T. Kaminou, T. Ogawa; Yonago/JP  
Keywords: Pathology, Image verification, Dementia, Technology assessment, Statistics, Experimental investigations, Nuclear medicine conventional, MR, Nuclear medicine, Neuroradiology brain, CNS  
DOI: 10.1594/ecr2013/C-1200
Purpose

Neuromelanin is a dark pigment that locates within certain catecholamine neurons of the human brain, such as the dopaminergic neurons of the substantia nigra pars compacta (SNC) and the noradrenergic neurons of the locus ceruleus (LC). It is thought to be formed as a by-product of the catecholamine metabolism cascade via enzymatic and/or oxidative polymerization. Parkinson’s disease (PD) is characterized by the progressive loss of dopaminergic neurons that contain neuromelanin in the SNC and of noradrenergic neurons in the LC. Several pathological studies have shown the selective loss of ventral intermediate and lateral cell groups of the SNC in PD. Noradrenergic neurons are also lost in the LC of patients with Alzheimer’s disease (AD).

Sasaki et al. reported that neuromelanin magnetic resonance imaging (NmMRI) could visualize decreased signal intensity in regions that reflect the loss of neurons containing neuromelanin. They also reported that the signal intensity in the SNC and LC was greatly reduced on NmMR images from patients with PD. Several investigators subsequently reported that NmMRI can show a reduction in the contrast ratio and volume of the SNC.

The physiological analogue of noradrenaline, I-metaiodobenzylguanidine (MIBG), traces uptake and transports both in noradrenaline presynaptic sympathetic nerve terminals and in subsequent vesicular storage. Postganglionic presynaptic cardiac sympathetic nerve endings can be non-invasively assessed by MIBG scintigraphy as a reduction of MIBG uptake indicates postganglionic sympathetic dysfunction. Cardiac MIBG uptake is reduced in patients with Lewy body diseases such as PD, as well as dementia with Lewy bodies, and MIBG scintigraphy can also help to differentiate PD from other types of parkinsonism.

PD in its early stages can easily be mistaken for any number of disorders. AD can also be mistaken for PD. However, the prognosis is completely different among these disorders, and the choice of treatment strategy becomes very important. Because early differentiation of PD and other neurodegenerative parkinsonism is crucial, there is an important need to improve the diagnostic accuracy.

The purpose of this study was to determine the usefulness of these modalities for the diagnosis of PD and AD by analyzing changes in signal intensity in the SNC and LC and MIBG uptake in the left cardiac ventricle, and examined the results for correlations between NmMRI and MIBG scintigraphy findings.
Methods and Materials

Patients

We investigated patients who were initially suspected of PD and were finally confirmed PD or AD between December 2008 and April 2012. Both MR imaging and MIBG scintigraphy performed within 1 year thereafter were retrospectively evaluated. Probable PD and AD were diagnosed according to the criteria of the United Kingdom Brain Bank and National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, respectively. Patients with PD were assigned to groups with either early-PD or late-PD based on Hoehn and Yahr staging.\textsuperscript{15} Early-PD comprised stages I and II, and late-PD comprised stages III, IV and V.

Patients with symptomatic cerebrovascular diseases and other central nervous system disorders were strictly excluded from the NMRI evaluation and those with cardiac diseases, diabetes mellitus and/or medications that can interfere with MIBG uptake, were excluded from the MIBG scintigraphy assessment.

We finally enrolled 13 (5 men and 8 women), 31 (14 men and 17 women) and 6 (3 men and 3 women) patients with early-PD, late-PD and AD, respectively (Table 1). The age of each group of early-PD, late-PD and AD ranged from 59 to 85 years (mean±SD, 68.3±5.88), 59 to 83 years (mean±SD, 71.8±8.95), and 58 to 84 years (mean±SD, 75.7±9.52), respectively. The duration of the illness for early-PD, late-PD, and AD ranged from 0 to 9 years (mean±SD, 4.30±5.37), 2 to 27 years (mean±SD, 9.48±6.86), and 1 to 3 years (mean±SD, 2.5±3.00), respectively. We used the Hasegawa dementia scale revised (HDS-R)\textsuperscript{16} to determine cognitive impairment or dementia, which is similar to mini-mental state examination (MMSE) and has a total score of 30. HDS-R in patients with AD ranged from 6 to 17 (mean±SD, 12.8±4.76).

The control group of NMRI comprised 20 age-matched patients (5 men and 15 women, 64 to 87 years (mean±SD, 74.8±5.4)) without a history of motor and cognitive impairment and brain lesions on MR images during the same period. However, we did not obtain MIBG scintigraphy from the same age-matched patients during this period.

Our institutional review board approved the study and written, informed consent was waived.
Table 1: Clinical characteristics of patient and control groups. Age does not differ between patient and control groups ($p = 0.082$; one-way analysis of variance).

References: - Yonago/JP

**Image acquisition**

All MR images were acquired using a clinical 3T MR scanner (Signa EXCITE HD, GE, Milwaukee, WI, USA). Axial images were acquired parallel to the anterior commissure-posterior commissure line. T1-weighted fast spin echo sequences were applied to TmMRI with the following parameters: TR/TE, 600/13 msec; echo train length, 2; slice thickness, 2.5 mm with 1- mm intersection gaps; matrix size, 512 × 512; FOV, 220 mm; acquisition time, 12 min. The scan covered the area from the upper border of the midbrain to the inferior border of the pons. We excluded other coexisting central nervous system disorders using axial T1- and T2-weighted images, fluid attenuated inversion recovery images and diffusion-weighted images of the entire brain according to the following standard protocol for adult brain imaging at our hospital: T1-weighted spin-echo sequence, TR/TE, 600/15 msec; section thickness, 5 mm; FOV 220 mm; matrix 512 × 512; T2-weighted fast spin-echo sequence, TR/TE, 4000/90 msec; section thickness, 5 mm; FOV 220 mm; matrix 512 × 512; fluid attenuated inversion recovery sequence, TR/TE/IR, 4000/90/20; section thickness, 5 mm; FOV 220 mm; matrix 512 × 512; and diffusion-weighted imaging sequence, TR/TE, 4000/90 msec; section thickness, 5 mm; FOV 220 mm; matrix 512 × 512; maximum b factor, 1000 mm$^2$/s.
The patients received an intravenous injection of 111 MBq of \(^{123}\text{I}\)-MIBG, and static planar images of the chest were acquired 30 min later for 4 min in a 256 × 256 matrix using a dual-head gamma camera with a large field of view and a low-energy, high-resolution collimator (E-CAM; Siemens, Erlangen, Germany).

**Image analysis**

Signal intensity was measured for quantitative NmMRI by setting ROIs. We equally divided into medial and lateral SNc at the level of the inferior colliculus and defined the ROIs in areas including the high signal intensity on NmMRI. We also defined the ROIs symmetrically in the ventral tegmentum as control located in the anterolateral part of aqueduct. Concerning LC, we defined the ROIs in the anterolateral areas around the fourth ventricle at the level of upper pons and also defined the ROIs symmetrically in the tegmentum as control located just behind the medial lemniscus. The sizes of the ROI were 8, 2 and 10 mm\(^2\) on the SNc, LC and tegmentum of the midbrain and pons, respectively. We calculated the contrast ratios of the three bilateral portions by dividing their signal intensity by that of control areas such as the tegmentum of midbrain and pons.

A ROI was drawn manually over the whole heart on MIBG scintigrams to assess the global myocardial kinetics of MIBG. A second rectangular ROI over the upper mediastinum served as a background reference region. The density of the MIBG count in the heart and the mediastinum and heart-to-mediastinum count ratios were calculated for the images.

**Statistical analysis**

Differences in contrast ratios between early-PD, late-PD, AD and controls in the medial SNc, lateral SNc and LC on NmMRI and between early-PD, late-PD and AD on MIBG scintigraphy were then statically analyzed. The medial SNc, lateral SNc, and MIBG scintigram were analyzed using a one-way analysis of variance and the Bonferroni post hoc test, and the LC was analyzed using the Kruskal-Wallis and Dunn post hoc tests. The level of statistical significance was defined as \(p < 0.05\) for all tests. The contrast ratios of NmMRI and MIBG scintigram in early-PD, late-PD and AD were analyzed using Spearman's rank-order correlation coefficient test.
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<table>
<thead>
<tr>
<th></th>
<th>early-PD</th>
<th>late-PD</th>
<th>AD</th>
<th>Control</th>
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<tr>
<td>Patients</td>
<td>13</td>
<td>31</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
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<td>I :3,:10</td>
<td>III:16,IV:12, V:3</td>
<td>/</td>
<td>/</td>
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<tr>
<td>Male/female</td>
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<td>14/17</td>
<td>3/3</td>
<td>5/15</td>
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<td>Age (y) mean ± SD</td>
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<td>71.8±8.95</td>
<td>75.7±9.52</td>
<td>74.8±5.41</td>
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<tr>
<td>Duration (y) mean ± SD</td>
<td>4.30±5.37</td>
<td>9.48±6.86</td>
<td>2.5±3</td>
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<tr>
<td>Hasegawa dementia</td>
<td>/</td>
<td>/</td>
<td>12.8±4.76</td>
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<tr>
<td>scale-revised mean ± SD</td>
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Results

The signal intensity of the lateral SNc on NmMRI was reduced in early-PD and late-PD and that of the medial SNc was gradually and stage-dependently reduced in PD. The signal intensity of LC was obviously reduced in late-PD. Signal reduction was not significant in the SNc and LC of patients with AD (Figure 1a). The heart-to-mediastinum ratio on MIBG scintigrams was stage-dependently reduced in PD and normal in AD (Figure 1b).

Fig. 1: Findings of NmMRI and MIBG scintigrams of patients and controls a.NmMRI: Signals are reduced in NmMR images of SNc and LC according to PD stage. b.MIBG scintigraphy: MIBG scintigrams show PD stage-dependent cardiac MIBG reduction

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Quantitative NmMRI revealed smaller contrast ratios in the lateral SNc of patients with early-PD than in that of control patients, and in that of patients with late-PD than in that of patients with AD and controls (p < 0.05) (Figure 2a). The contrast ratios of the medial SNc were smaller in patients with early-PD than in controls, and in patients with late-PD than in those with early-PD, AD and controls (p < 0.05) (Figure 2b). Contrast ratios in the LC of patients with late-PD were smaller than in control patients (p < 0.05) (Figure 2c). Signals were not significantly reduced in the SNc and LC on NmMR images of patients with AD compared with controls.
The heart-to-mediastinum count ratio on MIBG scintigram was stage dependently reduced in patients with PD (p < 0.05), and normal (mean ± SD, 2.15 ± 0.15) in those with AD (mean ± SD, 2.19 ± 0.40) (Figure 2d).

Fig. 2: Box and whisker plots of signal intensity ratios on NmMR images and heart-to-mediastinum count ratios on MIBG scintigrams in patients with PD, Alzheimer's disease and controls. Horizontal bars in boxes show median values. a. lateral SNc, b. medial SNc, c. LC, d. MIBG *p < 0.05.

References: - Yonago/JP
Signal intensity ratios in the SNc on NmMRI positively correlated with heart-to-mediastinum count ratios on MIBG scintigrams (Figure 3).
Fig. 3: Correlation between signal intensity ratio in medial SNc on NmMR image and heart-to-mediastinum count ratio on MIBG scintigram \( \rho=0.3984 \)

References: - Yonago/JP

Spearman's rank-order correlation coefficients in the medial and lateral SNc were 0.358 and 0.398 respectively, which reached statistical significance (Table 2).

<table>
<thead>
<tr>
<th>Spearman’s coefficient rate (( \rho ))</th>
<th>lateral SNc</th>
<th>medial SNc</th>
<th>LC</th>
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<tr>
<td>H/M ratio</td>
<td>0.3582</td>
<td>0.39841</td>
<td>NS</td>
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Table 2: Correlation between signal intensity ratio in medial SNc on NmMRI and heart-to-mediastinum count ratio on MIBG scintigraphy

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**Fig. 3:** Correlation between signal intensity ratio in medial SNc on NmMR image and heart-to-mediastinum count ratio on MIBG scintigram $r=0.3984$

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**Table 2:** Correlation between signal intensity ratio in medial SNc on NmMRI and heart-to-mediastinum count ratio on MIBG scintigraphy

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Conclusion

NmMRI~SNc~

We found that the contrast ratio of the lateral SNc was significantly decreased in early-PD and late-PD and that of the medial SNc gradually and stage-dependently decreased in PD, which corresponded to the pathological lesions. These findings indicate that SNc lesions extend from the lateral to the medial regions as PD progresses. Tanaka et al. reported that a reduction in neuromelanin contrast started ventrolaterally and advanced medially in the substantia nigra based on a visual assessment of NmMR images. However, the present study is the first effort to quantify medial and lateral SNc using NmMRI to the best of our knowledge.

NmMRI~LC~

Braak et al. proposed that alpha-synuclein-immunopositive Lewy neuritis and the accumulation of Lewy bodies that are characteristic pathological features of PD emerge from the inferior brain stem and ascend to the nuclear gray and cortical areas. However, some studies have also indicated that Lewy bodies and neural cell loss are irrelevant in some regions of the brain in patients with PD. Noradrenergic neurons are relatively well-preserved in the LC of patients with early-PD and they undergo different intracellular changes from the SN. Reports indicate that the signal intensity of the LC on NmMR images is significantly reduced in PD. We identified significant signal reductions in the LC of patients with late-PD, which suggests that lesions emerge in the LC during late-PD. These findings are compatible with the findings of others indicating that the LC plays a compensatory role for the substantia nigra during early-PD. Noradrenergic neurons containing neuromelanin in the LC are disrupted in AD, but the clinical or functional importance of such disruption remains unclear. Some reports suggest that a reduction in the number of noradrenergic neurons affects the accumulation of beta-amyloid, inflammation or microcirculation in the LC. Our NmMRI study could not identify a significant signal reduction in the LC of patients with AD. Busch et al. reported that the LC starts to lose cells only during the later stages of AD. Therefore, we consider that this result can be attributed to the relatively short duration (2.5 years) of the disease and the small number of patients with AD in this study. Signals were significantly more reduced in the medial and lateral SNc of patients with late-PD compared with AD, which is useful for differentiating these diseases.

MIBG
The neurological diseases with significant reduction in MIBG scintigraphy uptake include PD, dementia with Lewy bodies and pure autonomic failure, and they are recognized as characteristic findings of Lewy-body diseases. Sympathetic nerves in patients with PD are generally disturbed and Lewy bodies are found in sinoatrial nodal ganglia, the myocardium, and paravertebral ganglia. A pathological investigation has revealed that sympathetic nerve fibers are significantly reduced in patients with PD and well preserved in those with AD. Although the heart-to-mediastinum count ratio is reduced on MIBG scintigrams of early-PD, its relationship with progression remains controversial. We found here that the heart-to mediastinum count ratio was significantly lower in late-PD than early-PD, indicating that signal reduction is stage-dependent. On the other hand, we could not exclude the effect of a possible relationship between heart-to-mediastinum signal reduction and duration. The heart-to-mediastinum count ratio was well-preserved in patients with AD, which helped to differentiate it from late-PD.

**NmMRI vs. MIBG**

To the best of our knowledge, this is the first comparison of brain NmMRI and MIBG scintigraphy of PD and AD. We identified a weak correlation in the SNc, implying that the findings of both modalities can serve as indicators of progressive PD, which involves both the central and peripheral autonomic nervous systems. Our results revealed that the autonomic nervous system gradually becomes disturbed over time.

**Limitation**

The limitations of the present study are as follows. Because the study comprised very few patients with AD, further studies of a large population are required to validate our findings. Second, iron concentrations in the SNc that increase with age can mask signal alterations on NmMR images. Therefore, we could not exclude this effect when evaluating neuromelanin in elderly individuals. Third, the low spatial resolution of NmMRI did not allow three-dimensional image acquisition. Therefore, measurement errors might have arisen due to partial volume effects particularly when assessing changes in the LC.

**Conclusions**

The SNc becomes disturbed from the lateral to the medial region on NmMR images of the SNc as PD progresses and the LC is also disturbed in late-PD. The sympathetic nerves in the left cardiac ventricle are also disturbed in MIBG scintigrams of PD. Thus, NmMRI and MIBG scintigraphy can be helpful tools to evaluate PD progression and to differentiate PD from AD.
References


Personal Information

Fuminori Miyoshi, Department of Radiology, Tottori University, Yonago, Japan
fuminori_113344@hotmail.com

Shinichiro Kitao, Department of Radiology, Tottori University, Yonago, Japan
sskitao@yahoo.co.jp

Marie Takasugi, Department of Radiology, Tottori University, Yonago, Japan
mtakasugi@med.tottori-u.ac.jp

Yuki Shinohara, Department of Radiology, Tottori University, Yonago, Japan
tis_clay@yahoo.co.jp

Yoshiko Kanasaki, Department of Radiology, Tottori University, Yonago, Japan
ykadota@aol.com

Shinya Fujii, Department of Radiology, Tottori University, Yonago, Japan
sfujii@med.tottori-u.ac.jp

Toshio Kaminou, Department of Radiology, Tottori University, Yonago, Japan
kaminout@med.tottori-u.ac.jp

Toshihide Ogawa, Department of Radiology, Tottori University, Yonago, Japan
ogawa@med.tottori-u.ac.jp