

## VIII 15. Occipital Glucose Metabolic Decrease by Donepezil Treatment Correlated with the Improvement of Visual Hallucinations in Dementia with Lewy Bodies: the Osaki-Tajiri Project

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### **Introduction**

Deficits in the neocortical cholinergic system are more pronounced in Dementia with Lewy bodies (DLB) than in Alzheimer's disease (AD)<sup>1</sup>, and are more severe in patients with hallucinations<sup>1,2</sup>. Treatment with cholinesterase inhibitor (ChEI) reduces the severity of hallucinations as well as improving general cognitive function<sup>1,3,4</sup>. Using technetium-99m hexamethyl-propyleneamine oxine (<sup>99m</sup>Tc-HMPAO) single photon emission tomography (SPECT), some authors showed the relationship between the improvement of visual hallucinations (VHs) and the increase of the occipital perfusion<sup>1,5</sup>. Mori et al.<sup>5</sup> reported serial cerebral blood flow (CBF) in DLB by <sup>99m</sup>Tc-HMPAO SPECT before and after donepezil treatment. They showed an increased regional CBF (rCBF) in lateral surface of bilateral occipital lobes corresponded to visual association cortices<sup>5</sup>. O'Brien et al.<sup>1</sup> compared how changes in brain perfusion over 1-year period were related to changes in the severity of core features of DLB, and found a significant correlation between an increase in perfusion in midline posterior cingulate and decrease in the severity of VHs. In the O'Brien's study, the duration of donepezil intake was not controlled, so the authors suggested that the effect of donepezil of the reduction in VHs was likely to be in part.

In order to ascertain the functional alteration of occipital cortex by the treatment with ChEI, we performed the investigation of the metabolic and symptomatic changes during donepezil treatment in DLB with VHs using FDG-PET.

## **Methods**

### *Participants*

The study included 13 patients (age  $80.0 \pm 4.0$  years; 7 women) with DLB with VHs, who were living with a responsible caregiver. The diagnosis of DLB was established by consensus of 2 experienced clinicians according to consensus guidelines<sup>6</sup>. All participants fulfilled diagnostic criteria for probable DLB, but, because of the nature of this study, a history of VHs was a mandatory inclusion criterion<sup>5</sup>.

After the first PET scan, all patients were treated for 12 weeks with donepezil according to Japanese dosing guidelines<sup>5</sup>. Donepezil was commenced at 3 mg/day. After 2 weeks, patients were reassessed for adverse effects. Patients who were tolerating then had their dose titrated up to 5 mg/day for remaining 10 weeks. The second PET scan was performed approximately 3 months after the first one.

For the neuropsychological assessment, the Mini-Mental State Examination (MMSE), and the category-B (Hallucination) of the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) were administered at baseline and 12 weeks. MMSE was used for the assessment for global cognitive function. The category-B (Hallucination) of BEHAVE-AD was used for the assessment of VHs (VH score).

### **PET data acquisition**

The PET study was performed using a model SET 2400W scanner (Shimadzu, Kyoto, Japan; axial) under resting condition with eyes opened. This scanner acquires 63 image slices at a center-to-center interval of 3.125 mm and has a spatial resolution of 3.9 mm full width at half maximum (FWHM) and a Z-axis resolution of 6.5 FWHM at center of field of view<sup>7</sup>. The PET room was kept lighted and quiet. A short cannula was placed in a cubital median vein for blood sampling. Transmission scan (6 minutes (min)) was performed with a <sup>68</sup>Ge/<sup>68</sup>Ga external rotating line source, approximately 30 min after an intravenous bolus injection of 185 MBq of <sup>18</sup>F-FDG. 40 min after the injection, 2D emission scan (10 min) was performed for quantitative analysis followed by 3D emission scan (5 min). A blood sample was collected at 40 min after the injection and <sup>18</sup>F radioactivity was measured with a well-type scintillation counter. The plasma glucose concentration was also measured 40 min after the injection. The time activity curve was estimated from the plasma radioactivity according to a simplified method<sup>8</sup>. The same procedure was used in a post-treatment PET scan.

## **Image analyses**

### *ROI method*

Cerebral metabolic rates for glucose (CMR<sub>glc</sub>) parametric image were obtained from each 2D image by the autoradiographic method. Quantitative analyses were performed with conventional region of interest (ROI) settings using Dr. View/LINUX software (AJS, Japan). Circular ROIs (10 mm diameter) were placed on the cortical ribbon of medial and lateral occipital region on the CMR<sub>glc</sub> images. Two ROIs were placed on medial and lateral occipital lobe in each hemisphere on five serial slices (20 per each region). Regional CMR<sub>glc</sub> (rCMR<sub>glc</sub>) were obtained from mean values of ROIs placed on each region. The post-treatment CMR<sub>glc</sub> image was coregistered to the pre-treatment image by SPM2 (Wellcome Department of Cognitive Neurology, London, U.K.) in each participants, and was analyzed using common ROIs to eliminate possible rater's arbitrariness. The detailed methodology has been described previously<sup>9,10</sup>. The changes of rCMR<sub>glc</sub> were analyzed by the paired t-test. The normalized rCMR<sub>glc</sub> values by the cerebellar CMR<sub>glc</sub> were also used on account of intersubject variability.

## **Outcome**

The assessment of the change of VHS was performed using the score of category-B of BEHAVE-AD (VH score) at pre- and post-donepezil treatment. The changes of neuropsychological tests were analyzed by the Wilcoxon signed-ranks test. Spearman's rank correlation test was used to examine the correlation between change in VH score and that in occipital CMR<sub>glc</sub>.

## **Results**

### *Clinical outcome and changes in neuropsychological tests*

VHS in 6 participants were completely disappeared after donepezil administration. Figures 2 and 3 show the results of MMSE and category-B of BEHAVE-AD (VH score) at pre- and post-donepezil treatment, respectively. There were significant changes in VH score ( $p=0.009$ ). Among 13 participants, 10 participants showed the decreasing VH score, namely improvement of VH, at the post-donepezil treatment, 2 no change, and only 1 participant (Pt. 9) increasing score (worsening of VH). The change of MMSE was insignificant ( $p=0.579$ ).

### *ROI: Changes in rCMRglc*

The rCMRglc in medial occipital cortex was significantly decreased (mean±S.D.: pre 7.86±1.90; post 6.72±1.09 mg/100 g/min., p=0.044) though the decrease in lateral occipital cortex was insignificant (pre 6.52±1.89; post 5.71±1.08 mg/100 g/min., p=0.15). As for the correlation between changes in VH and rCMRglc in medial and lateral occipital cortex, the scatter plot graphs show a positive correlation between VH score and rCMRglc in medial and lateral occipital cortex (medial: rs=0.783, p=0.002; lateral: rs=0.716, p=0.006). About the VH score change, no significance was detected between the patients with increased and decreased rCMRglc in medial and lateral occipital cortex by donepezil treatment (medial: p=0.125, lateral: p=0.088).

### **Discussion**

The present PET study demonstrated that the VH in DLB patients was improved by donepezil treatment, and that the improvement was significantly correlated with the metabolic change of occipital cortices. The results of the present study are different, in the following two points, from those of two SPECT studies which investigated the correlation between the donepezil treatment for VHs and cerebral perfusion change: brain regions within the occipital lobe, and the increase or decrease of its perfusion. First, about the difference of brain regions, previous studies showed the alteration of cerebral perfusion at lateral surface of bilateral occipital lobes<sup>5)</sup> and right posterior cingulate gyrus<sup>1)</sup>. The latter region was included in our study, and we also observed metabolic change at left medial occipital lobe (BA 18) which belonged to a primary visual area. Second, the functional change of the present study was quite contrary to that of reported literatures: by the donepezil treatment, occipital metabolism was decreased in our study and its perfusion was increased in the literatures<sup>1,5)</sup>. We are surprised at the opposite result of cerebral metabolism/perfusion by the donepezil treatment between the present and previous two studies<sup>1,5)</sup>, but it is possible that this difference was caused by the analytic procedure. For the image analyses, Mori<sup>5)</sup> and O'Brien<sup>1)</sup> used the SPECT, and the quantitative assessment was not carried out.

We found a significant positive correlation between change in VH score and metabolic change in medial and lateral occipital cortex. Perry et al.<sup>2)</sup> reported that the extensive loss of cholinergic cells correlated with VHs in DLB. Imamura et al.<sup>11)</sup> revealed that the hypometabolism in the right posterior temporal and parietal areas was significantly

milder in DLB with VHs than in DLB without VH. They suggested that the hypometabolism in the primary visual cortex and the relatively preserved metabolism in the temporoparietal association cortices might be associated with the occurrence of VHs in DLB patients. A relatively higher glucose metabolism for the neuronal loss in occipital lobe may underlie the development of VH in DLB. Donepezil may be effective for VH by modifying this disproportion.

## References

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