

# Improvement of Visuo-spatial Function Assessed by Raven's Colored Progressive Matrices in Dementia with Lewy Bodies by Donepezil Treatment

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**Objective:** Donepezil is used to improve cognitive impairment of dementia with Lewy bodies (DLB). Visuo-spatial dysfunction is a well-known symptom of DLB. Non-verbal Raven's Colored Progressive Matrices (RCPM) were used to assess both visual perception and reasoning ability in DLB subjects treated with donepezil.

**Methods:** Twenty-one DLB patients (mean age, 78.7±4.5 years) were enrolled. RCPM assessment was performed at the time of starting donepezil and within one year after starting donepezil.

**Results:** There were significant improvements of RCPM in the total scores between one year donepezil treatment ( $p=0.013$ ), in both Set A score ( $p=0.002$ ) and Set AB score ( $p=0.015$ ), but trend in the Set B score ( $p=0.083$ ).

**Conclusion:** Donepezil is useful for improving visuo-spatial impairment in DLB, but not for problem-solving impairment.

**KEY WORDS:** Lewy body dementia; Cholinesterase inhibitors; Raven's Colored Progressive Matrices; Visual spatial processing.

## INTRODUCTION

Dementia with Lewy bodies (DLB) is the second most common neurocognitive disorder next to Alzheimer's disease (AD),<sup>1</sup> and it is characterized by complex visual hallucinations, progressive cognitive dysfunction, and parkinsonism.<sup>2</sup> Visual hallucination is one of the core features of DLB, present in 54% to 70% of DLB patients,<sup>3</sup> and is one of the factors that increases caregiver burden.<sup>4</sup> It has been reported that the visual hallucinations of DLB are caused by visuo-spatial, visuo-perceptual, or attention deficits.<sup>5</sup>

Cholinesterase inhibitors such as donepezil have been used to treat cognitive dysfunction and neuropsychiatric symptoms.<sup>6</sup> Several reports have shown that donepezil improves the symptoms associated with progressive cognitive dysfunction.<sup>7,8</sup> In addition, imaging studies have reported that donepezil also improves visual hallucina-

tions.<sup>9,10</sup> On the other hand, it is well known that visuo-spatial deficits are worse in DLB than in AD.<sup>8,11,12</sup> Cholinergic dysfunction in DLB is reported to be related to visual responses in the visual cortex.<sup>13,14</sup>

The non-verbal Raven's Colored Progressive Matrices (RCPM) test is a psychological tool used to assess both visual perception and reasoning ability.<sup>15</sup> The RCPM score is not affected by various physical disabilities such as aphasia, cerebral palsy, and deafness.<sup>16</sup> The RCPM score was reported to be lower in DLB than in AD in one observational study.<sup>17</sup>

From these, visuo-spatial function of DLB is impaired and is possible to be improved by cholinesterase inhibitors. To the best of our knowledge, there are no longitudinal studies of how donepezil affects visuo-spatial deficits assessed by RCPM in DLB subjects. The present study examined how donepezil affects visuo-spatial function, as assessed by RCPM, in DLB subjects.

## METHODS

### Subjects

Untreated DLB patients (n=21; mean age, 78.7±4.5 years) who were outpatients at Ehime University Hospital and Zaidan Niihama Hospital were enrolled. DLB sub-

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jects were diagnosed according to the diagnostic criteria for probable DLB<sup>2)</sup> and were living with at least one caregiver. Some patients had psychiatric symptoms, but they could receive neuropsychological tests. Demographic data of DLB subjects are shown in Table 1. All patients were right-handed and had no cerebral vascular lesions on head computed tomography or magnetic resonance imaging (MRI). Patients who had a past history of psychiatric disorders and severe cardiovascular disease were excluded. All participants were of unrelated Japanese origin and signed written, informed consent forms approved by the institutional ethics committees of Ehime University Graduate School of Medicine and Zaidan Niihama Hospital.

### Evaluation of DLB Symptoms

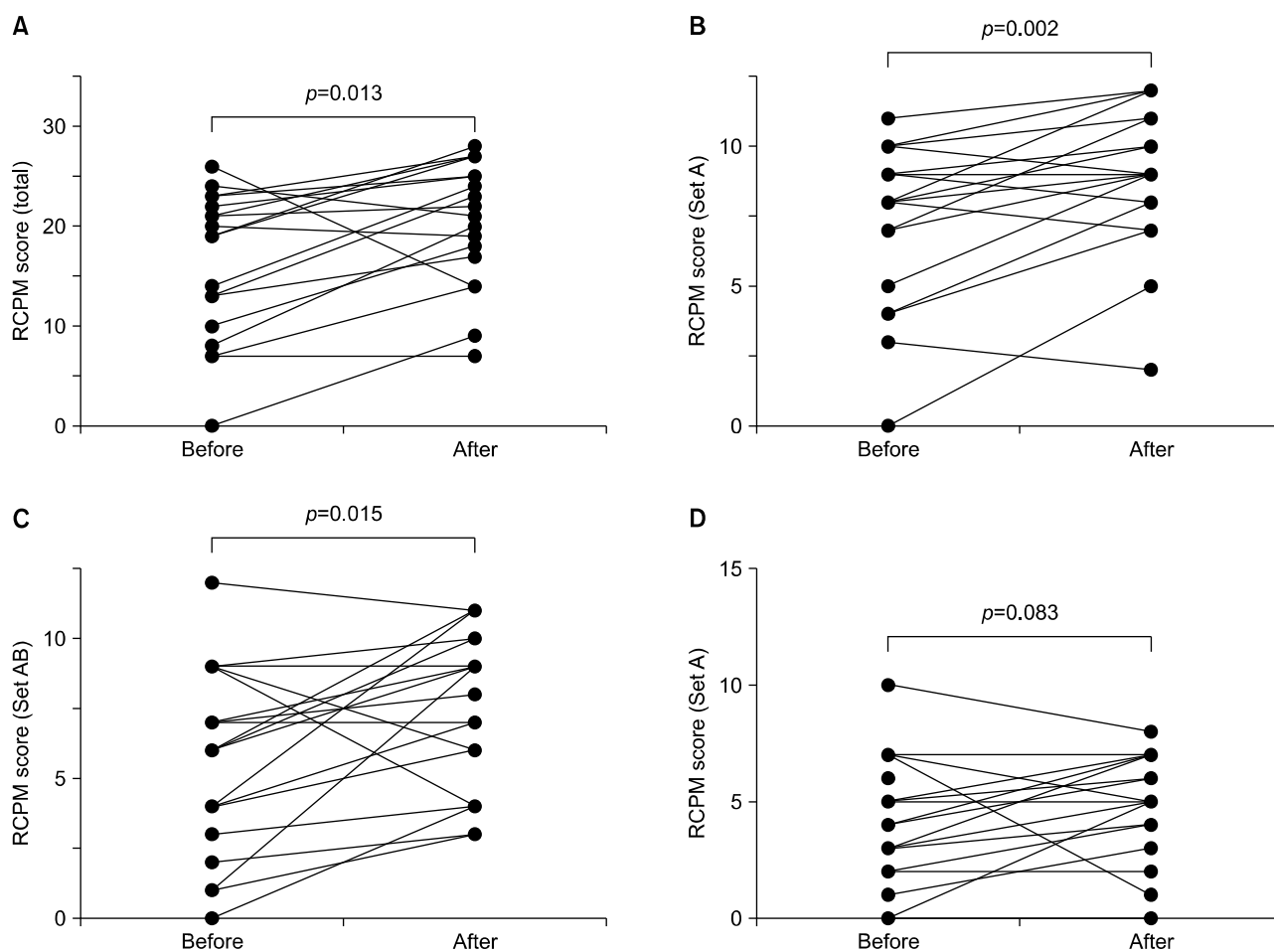
Cognitive impairments were evaluated by the Mini-Mental State Examination (MMSE).<sup>18)</sup> The severity of dementia was assessed by the Clinical Dementia Rating

(CDR). Neuropsychiatric symptoms were evaluated by the neuropsychiatric inventory (NPI) assessed by caregivers.<sup>19)</sup> We explained the method of RCPM to the participants and started the examination after they understood

**Table 1.** The demographic data and clinical data for DLB subjects

Characteristic	DLB subject
Subject (n)	21
Sex (n), male:female	6:15
Age (yr)	78.7±4.5
Age of onset (yr)	77.0±4.6
Duration of illness (yr)	1.7±1.4
Education (yr)	9.4±2.1
MMSE total score	20.2±6.1
NPI-10 total score	19.3±20.8
CDR score (0:0.5:1:2)	1:7:10:3

Values are presented as number only or mean±standard deviation. DLB, dementia with Lewy bodies; MMSE, Mini-Mental State Examination; NPI, neuropsychiatric inventory; CDR, Clinical Dementia Rating.



**Fig. 1.** The non-verbal Raven's Colored Progressive Matrices (RCPM) scores before and after taking donepezil. (A) Total score, (B) Set A score, (C) Set AB score, and (D) Set B score.

and concentrated it. The visuospatial deficit was evaluated by the RCPM.<sup>15)</sup> These clinical data are also shown in Table 1.

### Study Protocol

MMSE, CDR, NPI, and RCPM assessments were performed at the time of starting donepezil, and post prescribing RCPM was evaluated within one year after starting donepezil.

### Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics ver 22.0 software (IBM Japan, Tokyo, Japan). Comparisons of pre and post RCPM scores (total, Set A, AB, and B) were conducted by the Wilcoxon signed-rank test. Linear regression analyses were performed to ascertain whether age, age of onset, educational years, duration of illness, dose of donepezil, mean administration period (week), change of drugs without donepezil between pre and post RCPM test, MMSE, improved MMSE score, NPI, and CDR were associated with improved RCPM scores (total, Set A, AB, and B). Statistical significance was defined at the 95% level ( $p=0.05$ ).

## RESULTS

### Comparisons between Pre- and Post-RCPM Scores

There were significant improvements in the RCPM total score ( $p=0.013$ , Fig. 1A), Set A ( $p=0.002$ , Fig. 1B), and Set AB ( $p=0.015$ , Fig. 1C), but not in Set B ( $p=0.083$ , Fig. 1D). The details of the RCPM scores are shown in Table 2. The cut-off score of total RCPM score is 24/25 in Japanese version.<sup>20)</sup> According to this cut-off score, most patients had visuo-spatial dysfunction when pre RCPM test was conducted. The mean donepezil dose was  $5.1\pm 1.8$  mg, and the mean administration period was  $21.1\pm 12.4$  weeks. Some DLB subjects took other medications in pre-test (antipsychotics, one; antidepressants, two) and post-test

(antipsychotics, three; antidepressants, two; antiparkinson drugs, two).

### Linear Regression Analyses

Age, age of onset, educational years, duration of illness, dose of donepezil, mean administration period, change of drugs without donepezil between pre and post RCPM test, MMSE, improved MMSE score, NPI, and CDR were not significantly associated with improved RCPM scores for total, Set A, Set AB, and Set B scores.

## DISCUSSION

The results of the present study show that donepezil may improve RCPM scores in DLB subjects. Interestingly, Set A and Set AB scores were significantly improved, but not Set B scores. From linear regression analysis, the improvement was not associated with age, age of onset, duration of illness, dose of donepezil, MMSE, NPI, or CDR.

Let us first examine the improvements of the RCPM scores in detail. In the previous study, identity, similarity, and difference in Set A constitute the main relational features of the elements. In Set AB, spatial orientation such as symmetry or location is the predominant theme, while both logical and spatial principles in Set B are involved in figure construction.<sup>21)</sup> It appears that donepezil improves mainly spatial orientation involved with identity, similarity, and difference, which constitute the main relational features of elements in DLB subjects. However, logical thinking about spatial features was not improved by donepezil treatment. According to the study that divided the RCPM elements into visuo-spatial and problem-solving impairment,<sup>22)</sup> visuo-spatial impairment was improved, but problem-solving impairment was not improved by donepezil in the present study. Actually, Saumier *et al.*<sup>23)</sup> reported that the domains of visual-spatial motor abilities were improved by donepezil in AD subjects.

Second, let us examine the improvement of visuo-spatial function by donepezil. Anatomically, posterior cortical atrophy leads to visual-spatial dysfunction. A rodent study suggested that the pharmacological activation of acetylcholine receptors relates to the visual response.<sup>24)</sup> Cerami *et al.*<sup>25)</sup> using [<sup>18</sup>F]FDG-positron emission tomography (PET) and diffusion tensor imaging-MRI, reported that the occipital-parietal-frontal network could be at the basis of visuo-perceptual and visuo-spatial integration. It was reported that DLB is associated with cholinergic dysfunction on PET using radiolabeled acetylcholine analogues.<sup>26)</sup> In that study, the deficit was in the posterior

**Table 2.** The change of non-verbal Raven's Colored Progressive Matrices scores and Mini-Mental State Examination (MMSE)

Characteristic	Before (A)	After (B)	Improved score (B-A)
Total (n=21)	17.1±7.8	21.3±6.5	4.2±5.8
Set A (n=21)	7.4±2.8	9.0±2.4	1.6±2.0
Set AB (n=21)	5.8±3.3	7.5±2.7	1.8±3.1
Set B (n=21)	4.0±2.6	4.8±2.1	0.9±2.4
MMSE (n=16)	19.7±6.4	21.9±6.2	2.2±3.7

Values are presented as mean±standard deviation.

cortical regions, the inferior temporal gyrus, the supra-marginal gyrus, and the posterior cingulate. Tiraboschi *et al.*<sup>27)</sup> reported that cholinergic dysfunction is more marked in DLB than in AD. In addition, cerebral blood flow in the occipital cortex is increased by donepezil.<sup>9)</sup> From these studies, we assumed that visuo-spatial function was improved through the increased cerebral blood flow in the occipital cortex with donepezil treatment.

This study had several limitations. One limitation is that there may have been Type II error due to the small sample size. In addition, the effect of other medications could not be considered sufficiently due to small sample size. Second is that cognitive fluctuation of DLB was not assessed when conducting the RCPM test. Cognitive fluctuation is a well-known symptom in DLB, and it also has a significant effect on cognitive function and activities of daily living in DLB patients and causes an increased care burden for caregivers.<sup>28)</sup> Cognitive fluctuation may have affected the RCPM scores in the present study. In future studies, RCPM scores should be evaluated at the same time as cognitive fluctuation in a large sample. Third is that we did not recruit the control arm without donepezil. In future study, it is need to evaluate the improvement of RCPM scores with donepezil compared to control subjects without donepezil. Lastly, Ikeda *et al.*<sup>29)</sup> reported that MMSE score significantly improved compared to placebo in the 10-mg group, but not in 5-mg group. We had to increase the dose of donepezil because of the evidence of Ikeda *et al.*<sup>29)</sup> Even with low dose, the subjects showed significant improvement with donepezil treatment. The donepezil dose of DLB patients in this study is  $5.1 \pm 1.8$ . It is possible that higher dose of donepezil improve visuo-spatial function.

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