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Relationship between cerebral blood flow reduction patterns on scintigraphy and nonmotor symptoms in new-onset Lewy body disease

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Abstract

Background: This study aimed to investigate the relationship between patterns of reduced cerebral blood flow (CBF) evaluated by means of ^{123}I-N-isopropyl-p-iodoamphetamine ([^{123}I]IMP) scintigraphy and nonmotor symptoms in new-onset Lewy body disease (Parkinson's disease and dementia with Lewy bodies [DLB]).

Material and methods: Twenty-four patients diagnosed with new-onset Parkinson's disease or DLB underwent [^{123}I]IMP CBF scintigraphy at St. Marianna Medical University Hospital between January 1, 2010, and March 30, 2018. The reductions in CBF in various brain regions were analyzed using the three-dimensional stereotactic surface projection method and were compared to standard database values, yielding extent values (%). The extent values were evaluated in relation to the presence/absence of motor or nonmotor symptoms such as visual hallucinations, auditory hallucinations, delirium, depression, delusions, and dementia.

Results: The extent value was 100% in the angular, supramarginal, and lingual gyri; 95% in the orbital gyri; and 92.6% in the fusiform gyri. The extent value in patients without hallucinations and those with visual hallucinations was 41.2% and 54.3%, respectively, in the frontal lobe ($p = 0.02$) and 33.3% and 51.0%, respectively, in the medial prefrontal gyri ($p = 0.02$). Age-adjusted multivariate analysis showed that extent values in the frontal lobe were associated with visual hallucinations (odds ratio: 1.09, 95% confidence interval 1.00–1.18, $p = 0.04$).

Conclusions: The above results show that the CBF is reduced in several areas of the cerebral cortex and suggest an association between reduced blood flow in the frontal lobe and the appearance of visual hallucinations in patients with new-onset DLB.

KEY words: hallucinations; dementia with Lewy bodies; radionuclide imaging

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Introduction

Lewy body disease, an umbrella term encompassing Parkinson's disease (PD) and dementia with Lewy bodies (DLB), is reported to occur in about 1 in 1000 adults [1]. This disease develops owing to the deposition of alpha-synuclein aggregates, called Lewy bodies, in the brain, resulting in neuronal damage. In PD, Lewy body deposits are limited to the brain stem, whereas in DLB, the deposits extend to the cerebral cortex, subcortex, and peripheral neurons [2,3]. Between 8% and 40% of patients with PD experience visual hallucinations during the course of the disease [4].

^{18}Fluorine-labeled fluorodeoxyglucose positron emission tomography ([^{18}F]FDG PET) is widely used to diagnose functional cognitive impairment and has been reported to be useful for the diagnosis of visual hallucinations associated with DLB [5]. However,

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in Japan, [^{18}F]FDG PET is not routinely used to diagnose Lewy body disease or Alzheimer's disease. Instead, these are commonly diagnosed by means of cerebral blood flow (CBF) scintigraphy [6]. The extent of CBF reduction associated with PD has been shown to differ between Hoehn and Yahr (H&Y) stages [7]. In addition, both patients with Alzheimer's disease and those with DLB exhibit reduced [^{18}F]FDG metabolism in the temporoparietal junction, posterior cingulate gyri, precuneus, and medial occipital lobe [8]. The cingulate island sign is useful for distinguishing DLB from Alzheimer's disease on [^{18}F]FDG PET [6] and has been shown to be an excellent discriminator between Alzheimer's disease and DLB when assessed using ^{99m}Tc-L-ethyl cysteinate dimer CBF scintigraphy and the easy Z-score imaging system (eZIS; FUJIFILM Toyama Chemical Co., Ltd, Tokyo) analysis software [9].

[^{123}I]IMP scintigraphy is used for CBF evaluation. Three-dimensional stereotactic surface projection (3D-SSP) is commonly used to improve the diagnostic accuracy of PET and single-photon emission computed tomography (SPECT) [10]. In a previous study incorporating 3D-SSP, CBF values obtained from [^{123}I]IMP scintigraphy were compared statistically to those from a normal database and those from a CT-based attenuation correction normal database [11]. The cerebral metabolic changes associated with PD and those associated with Alzheimer's disease can be distinguished by means of 3D-SSP [12]. However, few studies have examined the relationship between nonmotor symptoms and CBF in patients with new-onset Lewy body disease. In addition, reports on CBF reductions related to dementia associated with PD and DLB are scarce. Moreover, there have been few attempts to quantify CBF in patients with PD dementia and in those with DLB.

In this study, we examined the patterns of CBF reduction in patients with new-onset Lewy body disease by using [^{123}I]IMP scintigraphy and compared the findings based on the presence or absence of motor and nonmotor symptoms.

Material and methods

Ethical considerations

This retrospective study was approved by the Ethics Committee of St. Marianna Medical University Hospital, Kawasaki, Japan (approval no. 4019). Patients were given the opportunity to opt out through the hospital website and in the hospital.

Patients

Image interpretation terminals and electronic medical records were searched for patients diagnosed with new-onset PD or new-onset DLB who underwent [^{123}I]IMP CBF scintigraphy at St. Marianna Medical University Hospital between January 1, 2010, and March 30, 2018.

All patients were evaluated by neurologists and psychiatrists. PD was diagnosed on the basis of the UK Parkinson's Disease Society's Brain Bank diagnostic criteria [13], and DLB was diagnosed according to the clinical diagnostic criteria proposed by McKeith et al. [14]. Nonmotor symptoms were diagnosed on the basis of the Unified Parkinson's Disease Rating Scale, Part 1, items 1, 2, and 3 (with a score above 1 indicating the presence of symptoms) [15].

At the time of [^{123}I]IMP CBF scintigraphy, 16 of the 24 patients included in the study were being treated with levodopa and carbidopa hydrate in combination (n = 9), levodopa (n = 2), ropinirole hydrochloride (n = 2), selegiline (n = 1), or donepezil hydrochloride (n = 2).

CBF scintigraphy and 3D-SSP imaging

Immediately after injection of 111 MBq [^{123}I]IMP (Nihon Medi-Physics Co., Tokyo, Japan), SPECT was performed with a triple detector system (GCA-9300, Canon Medical Systems, Ohtawara, Japan) equipped with a fan-beam collimator. Image reconstruction was performed with a ramp filter and Fourier back projection. The [^{123}I]IMP scintigraphy CBF values were compared to normal CBF values derived from 3D-SSP images. The 3D-SSP database was derived from 34 volunteers (17 men and 17 women, aged 61.7 ± 8.0 years).

We calculated the CBF reductions in various brain regions by comparing CBF values obtained in our patients against normal reference values. The CBF reduction was calculated as follows: number of pixels exceeding the threshold number in a region/number of pixels in that region. The threshold values were considered abnormal when the Z-score (Z-score = [normal group mean voxel — case voxel]/[normal group standard deviation]) was greater than 2, which is quite close to the commonly used threshold value of 1.96 [16]. When differences were observed between the left and right cerebral hemispheres, the larger value was selected for analysis.

Data and statistical analyses

For the purpose of the study, we compared the extent values of each brain region between patients with PD and those with DLB. We also compared the extent values within each brain region in relation to the presence vs absence of nonmotor symptoms, such as visual hallucinations, auditory hallucinations, delirium, depression, delusions, and dementia, and in relation to the presence vs absence of motor symptoms, such as rigidity, tremors, abnormal postural reflex, hypokinesia, mask-like facies, and short-stepped gait.

Median values were calculated, and between-group differences were analyzed by means of a Mann–Whitney U test. Univariate and multivariate analyses were conducted to identify factors associated with visual hallucinations. All analyses were performed with EZR, a statistical analysis software program developed at Jichi Medical University's Saitama Medical Center (Jichi Medical University's Omiya Hospital). P-values < 0.05 were considered statistically significant.

Results

Clinical characteristics of the study patients are summarized in Table 1. The total group comprised 14 men and 10 women, aged 41–86 years (median, 75 years), with new-onset PD (n = 15) or new-onset DLB (n = 9). Patient distribution according to the H&Y stages was as follows: stage I, n = 3; stage II, n = 6; stage III, n = 11; and stage IV, n = 4. Motor symptoms were noted in the following proportions of the study cohort: rigidity, 58.8%; tremors, 50.0%; abnormal postural reflex, 12.5%; hypokinesia, 8.3%; mask-like facies, 54.1%; and short-stepped gait, 45.8%. Nonmotor symptoms were noted in the following proportions of the study cohort: visual hallucination, 25%; auditory hallucinations, 4.1%; delirium, 12.3%; depression, 16.4% 1 patient had a past history and received therapy; delusions, 8.2%; and dementia, 71%.

Table 1. Patient clinical characteristics (n = 24)

Age (median [range]; years)	75 [41–86]
Sex ratio (male/female)	14/10
Parkinson disease/Lewy body dementia	15/9
Hoehn and Yahr stage I/II//III/IV	3/6/11/4
Motor symptoms	
Rigidity (%)	58.8
Tremors (%)	50.0
Abnormal postural reflex (%)	12.5
Hypokinesia (%)	8.3
Mask-like facies (%)	54.1
Short-stepped gait (%)	45.8
Nonmotor symptoms	
Visual hallucinations (%)	25
Auditory hallucinations (%)	4.1
Delirium (%)	12.3
Depression (%) (1 patient had a history of depression)	16.4
Delusions (%)	8.2
Dementia (%)	71

Data are presented as numbers or percentages, unless otherwise indicated

The extent values per lobe and per respective gyri for the total patient group are summarized in Table 2. Of the four cerebral lobes, the occipital lobe showed the greatest CBF reduction (at 89.6 ± 18.1%). Among the cerebral gyri, the angular (98.9 ± 4.23%), supramarginal (98.8 ± 4.00%), and lingual gyri (91.9 ± 15%) showed the greatest extent values, with all three values reflective of a mean decrease in the extent values of 90% or more. The distribution of notable extent values in the occipital lobe in patients with PD and those with DLB is shown in Figure 1. The extent value in the occipital lobe was significantly greater in patients with DLB than in those with PD (99.9% vs 91.5%; p = 0.01; Figure 1 — left panel). Additionally, compared to patients with PD, patients with DLB had significantly greater extent values in the posterior cingulate cortex (77.3% vs 32.7%; p < 0.01; Figure 1 — middle panel) and precuneus (74.8% vs 59.5%; p = 0.03; Figure 1 — right panel). There were no significant differences in the extent values in other brain regions according to the presence or absence of the following nonmotor symptoms: auditory hallucinations, delirium, depression, delusions, and dementia.

The distribution of notable extent values in patients with and without visual hallucinations is shown in Figure 2. The prevalence of visual hallucinations was 0% among patients with PD (0/15) and 66.7% among those with DLB (6/9). In the frontal lobe, the extent value was 41.2% in patients without visual hallucinations and 54.3% in patients with visual hallucinations (p = 0.02; Figure 2 — left panel). In the medial frontal gyrus, the extent value was 33.3% in patients without visual hallucinations and 51.0% in patients with visual hallucinations (p = 0.02; Figure 2 — right panel). More specifically, in the right medial frontal gyrus, the extent value was 27.2% and 48.4% in patients without and with visual hallucinations, respectively (p = 0.01); in the left medial frontal gyrus, the extent value was 28.1% and 51.0% in patients without and with visual hallucinations, respectively (p = 0.01). No significant difference in the extent values in any other brain region was found between patients without and with visual hallucinations.

In quantifying the relationship between extent values and visual hallucinations, both univariate and age-adjusted multivariate analyses (stepwise regression) showed reduced CBF in the frontal lobe to be statistically significant (odds ratio [OR]: 1.09, 95% confidence interval [CI] 1.00–1.18; p = 0.04; Table 3). Age, sex, H&Y stage, presence of PD vs that of DLB, and use of cholinesterase inhibitors or anti-Parkinson agents were not associated with visual hallucinations. Moreover, both univariate and age-adjusted multivariate analyses (stepwise regression) showed reduced CBF in the right, left, or both frontal lobes specifically and in the medial frontal gyri (right, left, or both specifically), with that in the right frontal lobe being statistically significant (OR: 1.09, 95% CI 1.01–1.18, p = 0.04; Table 4).

Discussion

In this study, we examined the patterns of CBF reduction in patients with new-onset Lewy body disease and compared the findings based on the presence or absence of motor and nonmotor

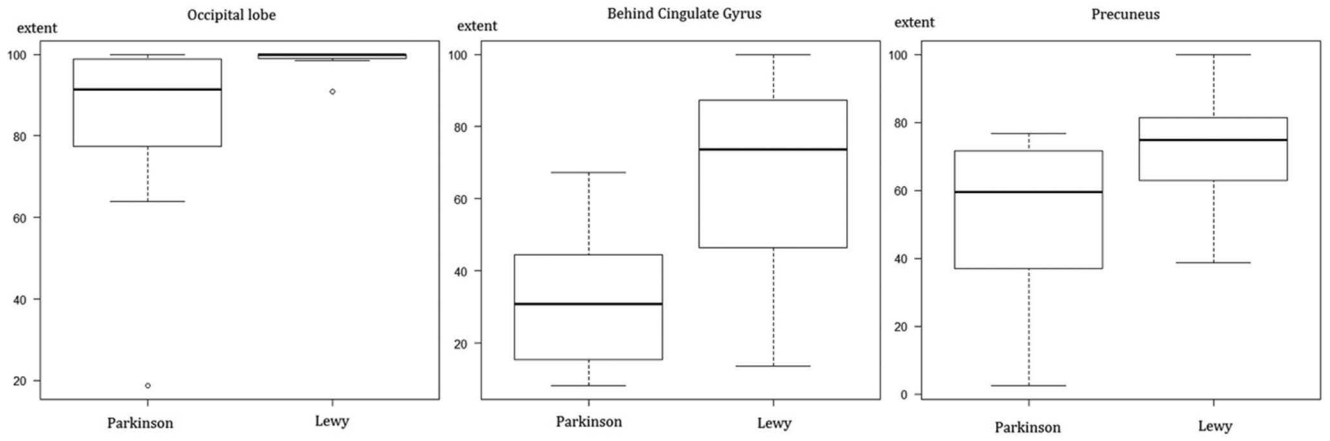

Figure 1. Box and whisker plots of the extent values for patients with Parkinson disease and patients with Lewy body disease

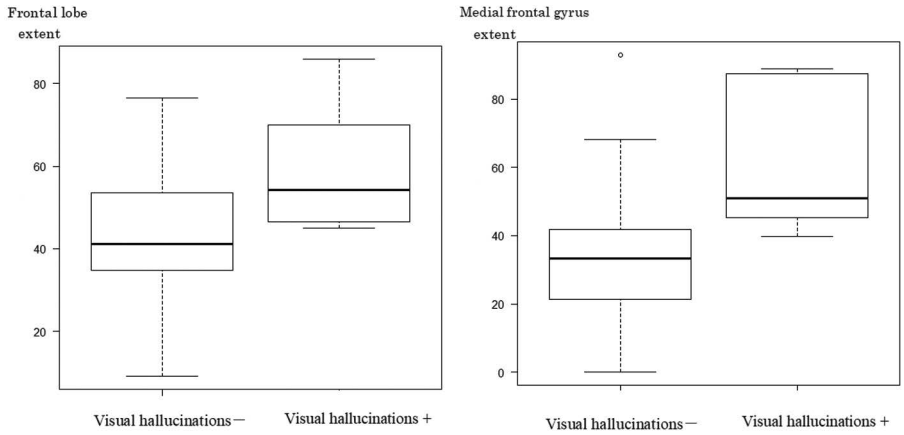

Figure 2. Box and whisker plots of the extent values in the frontal lobe and medial frontal lobe for patients with and without visual hallucinations

Table 2. Extent values per lobe and respective gyri

	Extent Value (%)
Frontal lobe	45.4 ± 18.1
Orbital gyri	71.8 ± 39.1
Gyri recti	51.9 ± 33.3
Parietal lobe	64.3 ± 17.4
Angular gyri	98.9 ± 4.23
Precuneus	58.6 ± 25.6
Supramarginal gyri	98.8 ± 4.00
Temporal lobe	80.2 ± 18.0
Fusiform gyri	84.5 ± 16.0
Occipital lobe	89.6 ± 18.1
Lingual gyri	91.9 ± 15.1
Anterior cingulate gyri	35.2 ± 29.6
Posterior cingulate gyri	47.1 ± 26.8

Data are presented as mean ± standard deviation

symptoms. Our results showed that the CBF is reduced in several areas of the cerebral cortex in these patients. Furthermore, our findings suggest an association between reduced blood flow in the frontal lobe and the appearance of visual hallucinations in patients with new-onset Lewy body disease.

There have been several reports on CBF scintigraphy in patients with PD and those with DLB. Patients with H&Y stages I–II disease were found to exhibit reduced CBF in the gray matter (reduced diffusion), hippocampus, and right temporal lobe inferior horn, whereas those with H&Y stages III–IV disease were found to exhibit reduced CBF in the cerebrum overall and relatively increased CBF in the left and right thalamus, globus pallidus, hippocampus, dentate nucleus, and right insular cortex [7]. DLB has been shown to be characterized by reduced [^{18}F]FDG metabolism in the temporoparietooccipital lobe [8]. Patients with DLB, compared to patients with Alzheimer's disease, exhibit more prominently reduced CBF in the two occipital lobes and in the left temporal lobe [17]. Patients with DLB exhibit what appears to be decreased CBF in the

Table 3. Results of univariate and multivariate analyses (stepwise regression) for identification of factors associated with visual hallucinations

	Univariate Analysis			Multivariate Analysis		
Factor	OR	95% CI	p value	OR	95% CI	p value
Age	1.32	1.02–1.72	0.03	1.47	0.99–2.19	0.06
Sex	1.57	0.25–10.1	0.63			
H&Y stage (0–II vs III–IV)	0.50	0.08–3.27	0.47			
Use of a cholinesterase inhibitor or anti-Parkinson agent	0.14	0.02–1.09	0.06			
PD or DLB	NA	NA	NA			
Frontal lobe	1.07	0.99–1.15	0.06	1.09	1.00–1.18	0.04
Parietal lobe	1.07	0.99–1.16	0.08			
Temporal lobe	0.97	0.93–1.02	0.27			
Occipital lobe	1.68	0.68–4.13	0.26			

CI — confidence interval; H&Y— Hoehn and Yahr; LBD — Lewy body disease; NA — not available; OR — odds ratio; PD — Parkinson's disease

Table 4. Results of the univariate and multivariate analyses (stepwise regression) for visual hallucinations related to the frontal lobe (right, left, both) and medial frontal gyri (right, left, both)

	Univariate analysis			Multivariate analysis		
Factor	OR	95% CI	p value	OR	95% CI	p value
Age				1.52	0.98–2.32	0.05
Frontal lobe (right)	1.06	1.00–1.13	0.07	1.09	1.01–1.18	0.04
Age				1.41	0.95–2.05	0.08
Frontal lobe (left)	1.11	1.00–1.22	0.05	1.11	0.99–1.26	0.07
Age				1.48	1.01–2.15	0.04
Medial frontal gyri	1.05	1.00–1.09	0.05	1.07	0.99–1.15	0.06

CI — confidence interval; OR — odds ratio

occipital lobe [18] and reduced CBF in the occipital lobe, along with a relative increase in CBF in the deep white matter [19]. However, the actual CBF varies from reduced to normal in the frontal, parietal, temporal, and occipital lobes and in the basal ganglia [20]. In this study, we found reduced CBF in the orbital gyri, an area where reduced CBF has been found to correlate with the severity of Alzheimer's disease [21], which is thought to be related to Yakovlev's circuit involving the amygdala-thalamus-orbital gyri-anterior temporal lobe areas [21, 22]. In addition, there is some supporting evidence that the volume of the medial temporal lobe is better maintained in patients with Lewy body disease than in those with Alzheimer's disease [14]. A statistical parametric mapping analysis found reduced CBF in the supplementary motor area and showed that the CBF in the dorsolateral premotor cortex decreases as the severity of the disease [20]. The differences between these studies are thought to be due to non-uniform areas of functional decline, owing to differing assessment methods and differing disease-progression patterns in the selected cases. Although various tracers have been developed for PD and DLB, tracers that specifically bind to alpha-synuclein protein aggregates could help clarify the pathologies of these conditions and provide data for assessing treatments and prognosis.

A greater distribution of Lewy bodies in the temporal lobes is associated with a higher frequency of visual hallucinations [23]. Pathological examination of the brains of deceased patients with PD or DLB and of those who experienced visual hallucinations has shown the presence of large numbers of Lewy bodies in areas of the temporal lobe, such as the amygdala and parahippocampal gyri [23]. Furthermore, the presence of many Lewy bodies has been noted in the middle frontal, middle temporal gyri, transentorhinal, and anterior cingulate cortices of patients with visual hallucinations [24].

Moreover, visual hallucinations in patients with DLB have been linked to reduced CBF in the left ventral occipital gyrus and bilateral parietal areas [25]. In our study, compared to patients who did not experience visual hallucinations, patients with new-onset Lewy body disease who experienced visual hallucinations exhibited significantly lower CBF in the frontal lobe. In addition, the frontal lobe CBF was significantly lower in the medial prefrontal gyri in patients with visual hallucinations than in those without visual hallucinations, for reasons that are yet unclear. Reduced CBF affected the occipital lobe, temporal lobe, parietal lobe, and frontal lobe, in that order. These findings together with the link between Lewy bodies and visual hallucinations suggest that the presence of a large number of Lewy bodies in the frontal lobes may indirectly reflect the reduced frontal lobe CBF in patients with visual hallucinations. The appearance of visual hallucinations may be affected by reduced nerve function, not only in the occipital lobe but also in a wide area extending to the medial frontal area. The relationship between the reduced CBF in anterior brain regions and the higher brain dysfunction associated with these anterior regions needs to be clarified and the pathology of nerve fiber routes should be explored.

Z-scores used in this study were based on normal database values. The utility of Z-scores for ^{23}I-IMP SPECT imaging in the differentiation between Alzheimer's disease (AD) and DLB and other dementia and degenerative changes has been reported [26]. Furthermore, in cases of Alzheimer's dementia, Z-scores were shown to correlate inversely with the Mini-Mental State Examination and the Clinical Global Impression-Severity Illness scores [27]. Therefore, we believe our data are clinically meaningful.

Visual hallucinations are present in a substantial proportion of patients with PD, reportedly affecting 15.8% to 74% of patients, including some with recent-onset PD [28–30]. Notably, the frequency of visual hallucinations was reported to be 44.4% in DLB [31]. The occurrence of visual hallucinations among patients with DLB is marked and outweighs that among patients with PD (62.5% vs 20.0%) [32]. In a recent meta-analysis, the pooled prevalence of visual hallucinations was shown to be 28.2% and 61.8% among patients with PD and those with DLB, respectively [33]. Thus, the extreme difference in the prevalence of visual hallucinations between our study patients with PD and those with DLB is not unusual. As visual hallucinations can appear early in patients with PD, the occurrence of visual hallucinations is not relied upon for a differential diagnosis of DLB (vs PD). Nuclear imaging, however, appears to be reliable for distinguishing between the two diseases.

Our study was limited in that it was a single-center study that included a small number of patients. In addition, the disease had reached H&Y stage III or IV in some patients by the time of the scintigraphic examination, despite the study only including patients with new-onset Lewy body disease. Some of the patients were older adults, and the ability of these patients to perform activities of daily living was indeed impaired. Despite the mixed study group, our study showed that reduced CBF is observed in cases of DLB and in patients suffering hallucinations, regardless of the H&Y stage. The manifestations of

Lewy body disease vary depending on the version of the disease. There is the presence of heterogeneity and some subgroup variation in early-stage PD [34]. Multicenter prospective studies with larger numbers of patients are needed to confirm our findings.

Conclusions

In conclusion, the results of our study showed that the CBF is reduced in several areas of the cerebral cortex and suggest an association between reduced blood flow in the frontal lobe and the appearance of visual hallucinations in patients with new-onset Lewy body disease.

Conflict of interest

Yukinori Okada received the lecture fee from AstraZeneca and Beyer not applicable the COI value in Japan, and the authors of this work have nothing to disclose for this study.

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