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Regional Cerebral Blood Flow in Vascular Depression Assessed by ^{123}I-IMP SPECT

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Abstract

Objective: As the prevalence of white matter hyperintensities detected on T 2 weighted MRI scans in patients with late-onset depression is higher than that in nondepressed patients, the concept of "vascular depression" (VDep) was introduced in 1997. However, the pathology of vascular depression has not been clarified. This study examined the differences in functional imaging between vascular and non-vascular depression (non-VDep). **Methods**: We utilized ^{123}I-IMP single photon emission computed tomography (SPECT) to compare regional cerebral blood flows (rCBF) between 9 patients with VDep (Krishnan criteria) and 11 age- and sex-matched patients with non-VDep in both depressed and remitted states. **Results**: In both VDep and non-VDep patients, mean rCBF increased significantly as depression improved, partially aided by changes in left anterior temporal blood flow. In addition, compared to non-VDep patients, the left anterior frontal rCBF for VDep patients was significantly lower in both depressed and remitted states. **Conclusions**: Left anterior temporal rCBF therefore appears to represent a state marker that increases as symptoms associated with late-onset depression improve, regardless of vascular changes. Furthermore, in VDep patients, left anterior frontal rCBF was low in both states compared to non-VDep patients, and might not only represent a trait marker, but also correlated with the duration of disease and likelihood of recurrence and relapse. (J Nippon Med Sch 2003; 70: 321–326)

Key words: depression, cerebrovascular disease, single photon emission computed tomography (SPECT), regional cerebral blood flow (rCBF)

Introduction

Late-onset depression encompasses a high percentage of patients with cerebrovascular changes[1]. Several studies have reported that elderly patients with depression display white matter hyperintensities more frequently than nondepressed patients[2–5]. In 1997, Krishnan et al.[6] and Alexopoulus et al.[7] proposed the term "vascular depression" (VDep), as analogous to "vascular dementia" to categorize this subtype of depression occurring in the context of cerebrovascular disease. They suggested that the concept of VDep may have

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diagnostic, prognostic, and treatment implications. However, the mechanisms of VDep remain unknown. The majority of functional imaging studies in depressive disorders have been confined to depression without cerebrovascular changes[8,9], and have rarely focused on VDep.

The aim of the present study was therefore to investigate differences in regional cerebral blood flow (rCBF) patterns on recovery from depressed state between patients with VDep and non-VDep. We hypothesized that rCBF changes in recovery from VDep would differ from those in recovery from non-VDep.

Methods

The 20 subjects included in this study comprised senile and pre-senile inpatients from the Department of Neuropsychiatry at Nippon Medical School Hospital. All patients who met DSM-IV criteria[10] for major depressive disorder were right-handed and medicated by antidepressants (VDep; 2 patients received amitriptyline, 4 patients received imipramine, and 3 patients received mianserin, non-VDep; 3 patients received amitriptyline, 5 patients received imipramine, and 3 patients received mianserin). No patients displayed concurrent neurological or other medical illnesses or substance abuse. After informed consent was obtained, brain magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT) were performed during depressed state and after clinical recovery. Patients were divided into a VDep group (n = 9; 5 males, 4 females; mean age (± SD), 67.2 ± 11.3 years) and a non-VDep group (n = 11; 6 males, 5 females; mean age, 62.3 ± 8.1 years) on the basis of MRI examination. VDep was defined according to Krishnan criteria[6]. It used a modified Fazekas classification system[11], which provided a rough assessment of the extent of subcortical gray matter, deep white matter, and periventricular changes on brain MRI. Patients were classified as having VDep if a score of ≥ 2 on either deep white matter hyperintensity or subcortical gray matter ratings was obtained. Non-VDep patients displayed scores of 0 or 1 on both deep white matter hyperintensity and subcortical gray matter ratings. A single punctate lesion in deep white matter reflects perivascular space and was considered normal. The severity of depression was evaluated using the 17-item Hamilton rating scale for depression (HAM-D)[12] on the day of rCBF measurement. In addition, an HAM-D score of < 7 was used to define remission.

Imaging began 10 min after the injection of 222 MBq of [^{123}I]N-isopropyl iodoamphetamine. A tripple-headed gamma camera system (Prism 3000 Marconi Medical Inc) was utilized. Total scanning time and total number were of 60 sec/projection and 72 projections. Data were obtained on a 128 × 128 matrix. The SPECT data were reconstructed using filtered back-projection method. The prefilter setting was lowpass filter (order 8, cut off 0.30 cycle/cm), and the absorption correction was Chang's correction (0.08/cm).

For each subject, 24 transcoronal slices vertical to the A-P line were acquired. Four slices were obtained to evaluate rCBF in bilateral frontal, anterior cingulate, temporal, basal ganglia, thalamic and cerebellar regions. The rCBF was determined using regions of interest (ROIs) drawn manually and the regions outlined were the above areas. All ROIs were circular and 1.5 cm in diameter. A total of 38 ROIs per subjects were analyzed (**Fig. 1**). ^{123}I-IMP uptake ratios for each ROI were standardized using mean rCBF counts of whole brain obtained according to the autoradiography (ARG) method[13,14].

Statistical analysis was performed using two-way analysis of variance (ANOVA). A p-value below 0.05 was considered statistically significant.

Results

Table 1 presents clinical and demographical features for the VDep and non-VDep groups. No significant differences were observed in age, gender, age at onset, or antidepressant dosage (in both depressed and remitted states). VDep group patients displayed significantly longer duration of illness ($p < 0.05$) and tended to show higher frequencies of relapse and recurrence ($p < 0.1$) compared to the non-VDep group.

VDep group patients displayed significantly lower

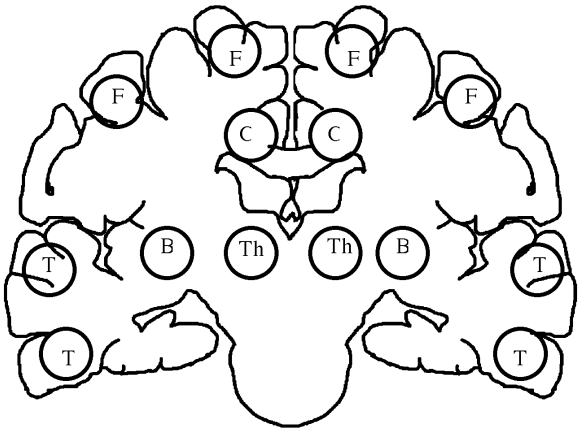

Fig. 1 This figure shows one of our four slices for rCBF analysis. We draw 14 ROIs on this slice (4 for posterior frontal (F), 4 for anterior temporal (T), 2 for anterior cingulated (C), 2 for thalamus (Th), and 2 for basal ganglia (B)). We draw 14 ROIs on just 1 slice after this slice, 4 ROIs on 7 slices anterior to this slice, and 6 ROIs on 5 slices posterior to this slice. We use 4 ROIs for anterior frontal, 8 ROIs for posterior frontal, 8 ROIs for anterior temporal, 6 slices for posterior temporal, 4 slices for anterior cingulate, 4 slices for thalamus, and 4 slices for basal ganglia.

Table 1 Demographic Characteristics

	VDep	non-VDep
Subjects (male/female)	9 (5/4)	11 (6/5)
Age (mean ± SD)	67.2 ± 11.3	62.3 ± 8.1
Age at onset (mean ± SD)	61.9 ± 9.8	56.1 ± 7.6
HAM-D (mean ± SD)		
depressed	30.1 ± 4.1	31.2 ± 3.6
remission	7.3 ± 0.3	7.0 ± 0.6
Length of episode (day)	88.0 ± 6.3*	67.2 ± 6.2
Dose of antidepressants[a)]		
Depressed state	81.8 ± 13.1	95.6 ± 23.1
Remitted state	82.7 ± 12.4	92.8 ± 24.0
Family history (%)	11.10	36.30
Relapse and recurrent (%)	66.6[+]	18.20

[a)] Imipramine equivalent dose
* $p < 0.05$, [+] $p < 0.1$

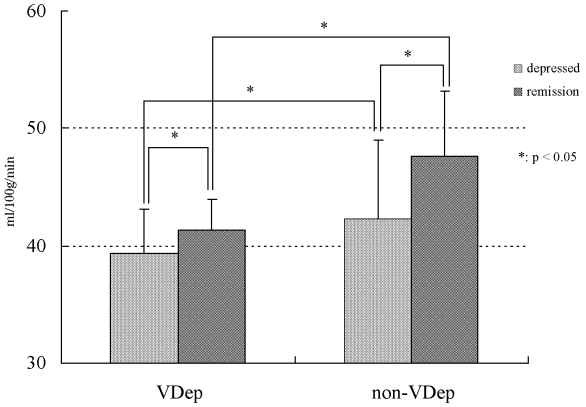

Fig. 2 Changes in mean rCBF for each group. VDep showed significantly lower mean rCBF than non-VDep during both depressed and remitted states. Furthermore, both VDep and non-VDep showed significantly higher mean rCBF in remitted state than in depressed state.

mean rCBF compared to the non-VDep group during both depressed and remitted states. Furthermore, both VDep and non-VDep groups showed significantly higher mean rCBF in the remitted state than in the depressed state (**Fig. 2**). Two-way ANOVA was performed to analyze the relationships between rCBF ratio and dependent variables such as diagnosis (VDep or non-VDep) and state (depressed or remitted). VDep group patients displayed significantly lower rCBF in the left anterior frontal region in both depressed and remitted states, compared to those in the non-VDep group. Both VDep and non-VDep groups displayed significantly increased rCBF in the left anterior temporal region in the remitted state compared to the depressed state (**Table 2**).

Discussion

The results of the present study showed that in both VDep and non-VDep patients, mean CBF increased as depression improved, partially aided by changes in left anterior temporal rCBF. In addition, left anterior frontal rCBF for VDep patients in depressed and remitted states was significantly lower than that for non-VDep patients.

Before discussing our study results further, it is important to mention the limitations to the methodology of the study. Firstly, no healthy individuals were investigated, and relative changes had to be compared between the two groups of patients with depression. Secondly, as all patients were on antidepressant medication, the effects of these drugs should have been considered. However,

Table 2 The mean rCBF ratios of each region between depressed and remission in VDep or non-VDep patients

region	depressed		remission		F ratio		
	VDep	non-VDep	VDep	non-VDep	state	diagnosis	interaction
LAF	0.95 ± 0.06	1.00 ± 0.05	0.93 ± 0.06	0.98 ± 0.04	1.2	8.1**	0.1
RAF	0.99 ± 0.07	1.00 ± 0.05	0.98 ± 0.06	1.00 ± 0.05	0.1	1.0	0.1
LPF	0.96 ± 0.05	0.97 ± 0.06	0.96 ± 0.04	0.96 ± 0.07	0.1	0.1	0.1
RPF	0.97 ± 0.52	0.99 ± 0.09	0.97 ± 0.05	0.98 ± 0.10	0.1	0.3	0.4
LAT	0.95 ± 0.03	0.95 ± 0.07	0.97 ± 0.05	1.00 ± 0.04	4.6*	1.2	0.2
RAT	0.99 ± 0.06	0.98 ± 0.04	1.00 ± 0.03	0.99 ± 0.05	1.2	0.9	0.3
LPT	0.98 ± 0.04	0.99 ± 0.03	0.98 ± 0.06	1.00 ± 0.04	1.4	1.2	0.2
RPT	1.01 ± 0.05	0.99 ± 0.04	1.00 ± 0.05	1.01 ± 0.06	1.8	0.6	0.1
LBG	1.03 ± 0.04	1.04 ± 0.07	1.04 ± 0.04	1.03 ± 0.04	0.1	0.1	0.4
RBG	1.06 ± 0.05	1.07 ± 0.06	1.08 ± 0.04	1.05 ± 0.06	0.1	0.3	1.4
LTHA	1.05 ± 0.10	1.05 ± 0.05	1.07 ± 0.05	1.04 ± 0.05	0.1	0.6	0.6
RTHA	1.09 ± 0.06	1.08 ± 0.06	1.10 ± 0.05	1.05 ± 0.07	0.4	3.1	0.7
LACIN	0.93 ± 0.04	0.94 ± 0.06	0.95 ± 0.07	0.97 ± 0.06	1.2	0.6	0.1
RACIN	0.94 ± 0.04	0.95 ± 0.07	0.94 ± 0.04	0.97 ± 0.06	0.5	1.3	0.1

AF: anterior frontal, PF: posterior frontal, AT: anterior temporal, PT: posterior temporal, BG: basal ganglia, THA: thalamus, ACIN: anterior cingulate

*: $p<0.05$, **: $p<0.01$ (two-factor ANOVA)

because antidepressant medications were administered in both depressed and remitted states, the effects on study results were considered minimal. Thirdly, we should consider the remote effect of cerebral infarction. It is well known that infarction decreases the rCBF in remote areas. Therefore, further study is needed to clarify the point that VDep patients have lower rCBF in the left anterior frontal lobe than non-VDep patients with comparable vascular lesions (i.e., size, number and cause of vascular lesions). We believe, however, that the lower rCBF in the left frontal lobe is the most significant characteristic of VDep patients, since many investigators have reported that the left anterior frontal area might be included in the mechanism of depression.

The most interesting finding in the present study was that left anterior frontal rCBF for VDep patients was lower than that for non-VDep patients. Robinson et al.[15, 16] reported that the prevalence and severity of depression after stroke was significantly associated with left anterior frontal lesions. In the present study, the location of vascular changes was investigated, and the results revealed that while vascular changes over the whole area in the white matter were observed in many patients, they were not concentrated in the left frontal region. These findings therefore suggest that decreased left anterior frontal rCBF does not directly lead to the formation of a lesion in a particular location, but that vascular changes in the white matter ultimately reduce left anterior frontal rCBF. In MRI-defined VDep, the onset mechanism of depression could be explained in terms of the accumulation of infarction beyond a depression threshold. This is referred to as a threshold hypothesis[7], but the results of the present study demonstrated that reduced left anterior frontal functions strongly correlated to the pathology of depression. Several studies on rCBF in patients with non-VDep unaccompanied by vascular changes suggest the involvement of reduced left frontal rCBF[17-19]. However, the results of the present study suggest that left anterior frontal rCBF for VDep was lower than that for functional depression.

In the present study, the length of disease duration for VDep patients was longer than that for non-VDep patients, and the prevalence of relapse and recurrence were higher for VDep patients. As far as rCBF research on depression is concerned, some studies have reported that left anterior frontal rCBF for patients with treatment-resistant or chronic depression is significantly lower than that

for non-depressed patients[20, 21]. These clinical characteristics for VDep could therefore be related to the finding that left anterior frontal rCBF for VDep patients in the remitted state was significantly lower than that for non-VDep patients.

The very interesting findings from this study were that when both VDep and non-VDep patients recovered from depression, left anterior temporal rCBF increased significantly. Mayberg et al.[22] investigated 5-HT2 binding in the left temporal cortex of patients with left hemisphere strokes, and reported that the lower the 5-HT 2 binding in the left temporal cortex, the more severe the depression. Furthermore, one study found that IMP activities in the left temporal region were lower than those in the right temporal region[23], while another study found that, in late-onset functional depression, severity of depression correlated with basal ganglia or front temporal perfusion[24]. The results of our study therefore suggest that changes in left anterior temporal rCBF may serve as an indicator for the recovery of depression in patients with VDep.

Conclusions

Unlike non-VDep, left anterior frontal rCBF for VDep is reduced irrespective of disease state, and this parameter could not only serve as a trait marker, but also correlate to the duration of disease and the likelihood of relapse and recurrence. In addition, regardless of vascular changes, left anterior temporal rCBF could represent a state marker that increases as symptoms associated with late-onset depression improve.

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