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Diagnostic Imaging of Higher Brain Dysfunction in Patients With Adult Moyamoya Disease Using Statistical Imaging Analysis for [^{123}I]Iomazenil Single Photon Emission Computed Tomography

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Abstract

[^{123}I]iomazenil (IMZ) is a specific radioligand for the central benzodiazepine (BZ) receptor that may be useful as a marker of cortical neuron loss after cerebral ischemia using single photon emission computed tomography (SPECT). This study used statistical imaging analysis for IMZ-SPECT to investigate the relationship between higher brain dysfunction and cortical neuron loss in the medial frontal lobes, to establish a confirmatory diagnosis of higher brain dysfunction in patients with adult moyamoya disease. IMZ-SPECT was estimated by three-dimensional stereotactic surface projections (3D-SSP). Cortical neuron loss was analyzed using the stereotactic extraction estimation (SEE) method (level 3: gyrus level) for 3D-SSP Z-score maps (Z-score >2). Extent of pixels with significant reduction of BZ receptor density within the target gyri (i.e. bilateral medial frontal gyri [MFGs] and anterior cingulate gyri [ACGs]) was calculated. In 6 patients with higher brain dysfunction, significant cortical neuron loss was observed in the bilateral MFGs in 4 patients, unilateral MFG in 1 patient, and bilateral ACGs in 2 patients. In 12 patients without higher brain dysfunction, no significant cortical neuron loss was observed in the bilateral MFGs or ACGs, and mild loss was observed in the bilateral MFGs in 2 patients, unilateral MFG in 4 patients, and unilateral ACG in 2 patients. Long-standing mild hemodynamic ischemia in the anterior circulation of patients with adult moyamoya disease could lead to incomplete brain infarction within the medial frontal lobes. Statistical imaging analysis using 3D-SSP and SEE methods for IMZ-SPECT could demonstrate significant cortical neuron loss in the bilateral frontal medial cortices involving MFG and/or ACG which correlate with higher brain dysfunction in patients with adult moyamoya disease.

Key words: higher brain dysfunction, moyamoya disease, three-dimensional stereotactic surface projections, iodine-123-iomazenil, single photon emission computed tomography

Introduction

Patients with adult moyamoya disease may suffer higher brain dysfunction[18] manifesting as cognitive impairments, such as memory, attention, performance, and social behavioral disturbances, which could become increasingly apparent.[8] Such cognitive impairments may occur in patients with medial frontal lobe damage including the anterior cingulate cortex.[1,19] In general, higher brain dysfunction associated with adult moyamoya disease could be detected by both neuropsychological findings and obvious medial frontal lobe damage visible on morphological neuroimaging such as computed tomography (CT) or magnetic resonance (MR) imaging. These patients should be supported by social welfare as psychologically handicapped persons. However, confirmatory diagnosis of higher brain dysfunction in patients with adult moyamoya disease without obvious medial frontal lobe damages on CT or MR imaging has not been established and could become a social

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Patients with moyamoya disease could suffer persistent hemodynamic ischemia in the anterior circulation. Atrophic changes of the frontal lobe are occasionally observed on CT or MR imaging. More recently, frontal cortical neuron damages involving incomplete brain infarction[4,17] could be estimated by functional neuroimaging using single photon emission CT (SPECT), because central benzodiazepine (BZ) receptor mapping using [^{123}I]iomazenil (IMZ)[2] is available for clinical use. IMZ is a specific radioactive tracer for the central BZ receptor that may be useful as a marker of cortical neuron loss after focal cerebral ischemia using SPECT.[7,17]

This study used statistical imaging analysis for IMZ-SPECT to investigate the relationship between higher brain dysfunction and the occurrence of incomplete brain infarction in the medial frontal lobes to establish confirmatory diagnosis of higher brain dysfunction in patients with adult moyamoya disease.[15]

Materials and Methods

Eighteen patients with adult moyamoya disease (3 males and 15 females with mean age of 39.3 ± 9.0 years) in the chronic stage were included in this study (Table 1). All patients had a clinical history of transient ischemic attack (TIA) or stroke episodes, and type of brain attack was classified as TIA, ischemic stroke, intraventricular hemorrhage (IVH), or intracerebral hemorrhage (ICH). Surgical revascularization was performed in 16 of the 18 patients, and long-term follow up was possible in all patients (Table 1). The outcome of TIA or other stroke in these patients was assessed by modified Rankin scale as 0–2, and daily life was independent at the time of study inclusion. Size of cortical infarction, subcortical white matter infarction, or brain injury associated with IVH or ICH in these patients was relatively small, and bilateral frontal brain atrophy was very mild on MR imaging in the 3 patients with higher brain dysfunction (Table 1). Hemodynamic cerebral ischemia was assessed by the dual table ARG method,[9] and territories of Stage 2 ischemia were not dominant in the anterior circulation, espe-

Table 1 Baseline characteristics of 18 patients with adult moyamoya disease

Case No.	Age (yrs)/ Sex	Type of attack	Lesions on MR imaging	Surgical revascularization	Follow-up period from attack
1	46/F	TIA + ISC	lt lateral frontal CoI	bil STA-MCA + EMS	17 yrs from TIA, 15 yrs from ISC
2	42/F	IVH + ISC + IVH	lt lateral frontal CoI, old IVH	bil STA-MCA + EMS	22 yrs from IVH, 15 mos from ISC, 11 mos from IVH
3	37/F	TIA + IVH	bil frontal subcortical WMI, lt parietal CoI, old IVH	bil STA-MCA + EMS	18 yrs from TIA, 3 mos from IVH
4	46/F	TIA	bil frontal mild atrophy	bil STA-MCA + EMS	7 yrs from TIA
5	58/F	TIA	bil frontal mild atrophy	bil STA-MCA + EMS	9 yrs from TIA
6	26/F	TIA	rt frontal subcortical WMI, bil frontal mild atrophy	bil STA-MCA + EMS	21 yrs from TIA
7	38/F	TIA	no definite lesion	rt STA-MCA + EMS	5 yrs from TIA
8	36/F	ICH	old ICH in rt basal ganglia	bil STA-MCA + EMS	5 yrs from ICH
9	30/F	TIA	bil frontal subcortical WMI, rt paraventricular MB	bil STA-MCA + EMS	6 yrs from TIA
10	36/F	ICH	old ICH in rt midbrain	rt STA-MCA + EMS	3 yrs from ICH
11	51/F	TIA + ICH	old ICH in lt basal ganglia	lt STA-MCA + EMS	42 yrs from TIA, 5 yrs from ICH
12	54/F	ICH	old ICH in lt basal ganglia	lt STA-MCA + EMS	4 yrs from ICH
13	31/F	IVH	old IVH, rt medial parietal CoI	bil STA-MCA + EMS	10 yrs from IVH
14	40/F	IVH + ICH	old IVH, old ICH in rt temporal lobe	bil STA-MCA + EMS	5 yrs from IVH, 1 yr from ICH
15	41/M	TIA	rt frontal subcortical WMI	bil STA-MCA + EMS	7 yrs from TIA
16	36/F	TIA	no definite lesion	not performed	2 yrs from TIA
17	34/M	IVH	old IVH	not performed	2 yrs from IVH
18	26/M	TIA	lt frontal WMI	bil STA-MCA + EMS	12 yrs from TIA

CoI: cortical infarction, EMS: encephalo-myo-synangiosis, ICH: intracerebral hemorrhage, ISC: ischemic stroke, IVH: intraventricular hemorrhage, MB: microbleeds, mos: months, STA-MCA: superficial temporal artery-middle cerebral artery bypass, TIA: transient ischemic attack, WMI: white matter infarction, yrs: years.

Table 2 Result of neuropsychological tests in 6 patients with higher brain dysfunction

Case No.	1	2	3	4	5	6
WAIS III (normal ≥80)						
full-scale IQ	66	85	88	82	98	58
verbal IQ	68	96	86	84	97	59
performance IQ	69	75	93	83	96	63
WMS-R (standard score: 100±15)						
general memory	90	78	84	84	110	80
attention and concentration	93	85	103	75	76	79
verbal memory	91	81	78	83	107	76
visual memory	92	74	81	94	109	101
delayed reproduction	92	60	89	102	114	80
Frontal function test						
trail making test-A	32	30	63	130	27	52
(standard time: sec)	(34)	(34)	(32)	(34)	(38)	(32)
trail making test-B	313	100	124	155	66	124
(standard time: sec)	(78)	(78)	(69)	(78)	(98)	(69)
verbal fluency test (/min)						
category fluency (normal ≥15)	15	14	10	19	21	19
''kana'' letter pick-up test	15/60	34/60	22/60	19/60	21/60	15/60
(standard response: number)	(36.6±10.0)	(36.6±10.0)	(42.4±8.6)	(36.6±10.9)	(31.9±10.9)	(44.1±9.4)
BADS						
total profile score	13/24	17/24	—	—	18/24	13/24
standardized score (normal ≥80)	75	95	—	—	98	75

BADS: behavioral assessment of the dysexecutive syndrome, IQ: intelligence quotient, WAIS-III: Wechsler Adult Intelligence Scale-Third Edition, WMS-R: Wechsler Memory Scale-Revised.

cially in the medial frontal lobe of all patients. No patients had hemodynamic compromise. The severity of hemodynamic cerebral ischemia was assessed as mild in all patients.

Relatively mild higher brain dysfunction, observed in 6 of the 18 patients, was confirmed by neuropsychological tests such as the intelligence test (Wechsler Adult Intelligence Scale-Third Edition: WAIS-III), memory test (Wechsler Memory Scale-Revised: WMS-R), frontal lobe function tests (trail making test part A and part B, verbal fluency test, ''kana'' letter pick-up test), and behavioural assessment of the dysexecutive syndrome (BADS) test. Higher brain dysfunction was defined by combined assessment of neuropsychological tests using the following criteria: lower scores than normal in the WAIS-III test, or lower scores than standard on attention (concentration) or delayed reproduction in the WMS-R test, or marked deviation to each standard on 4 categories in the frontal lobe function test, or lower standardized scores than normal in the BADS test (Table 2).

Focal reduction of BZ receptor density indicated as decreased IMZ distribution could be a marker of cortical neuron loss. Projection data of IMZ-SPECT were obtained 3 hours after intravenous tracer injection, and IMZ 3-hour images equivalent to the distribution of BZ receptor density were reconstructed.[10] The IMZ 3-hour image could be estimated by statistical imaging analysis such as three-dimensional stereotactic surface projections (3D-SSP).[11] In this analysis, relative IMZ distribution of the cortex on 3D-SSP was compared with the normal database (n = 18), in which all pixels have both mean count value and standard deviation normalized by count value of reference regions such as global brain. Differences between individual data and the normal database in each pixel were converted to Z-score (multiple of standard deviation), then the cluster of pixels with significant difference (Z-score >2) could be identified as the target area with cortical neuron loss on Z-score maps (total 8 directions).

For assessment of cortical neuron loss in the frontal lobes, areas of cortical neuron loss around the medial frontal gyrus (MFG) and anterior cingulate gyrus (ACG) on Z-score maps were focused within the medial frontal lobe, and such areas around the superior frontal gyrus and middle frontal gyrus on Z-score maps were focused within the lateral frontal lobe by visual assessment (Tables 1 and 2). Clusters of pixels on Z-score maps (Z score >2) were defined as significant cortical neuron loss, and assessed as follows: ++, cortical neuron loss in multiple areas; +, cortical neuron loss in single area; and −, no area of cortical neuron loss. Group comparison was performed between the normal database and 2 patient groups (6 patients with higher brain dysfunction and 12 patients without higher brain dysfunc-

tion) to estimate common target areas of significant cortical neuron loss in the frontal lobes (Z-score >2).

For assessment of cortical neuron loss in the frontal medial cortex, cortical neuron loss was analyzed using the stereotactic extraction estimation (SEE) method (level 3: gyrus level analysis)[12,13] for Z-score maps (Z-score >2). Extent (%) of pixels with significant reduction of BZ receptor density within the target gyri (i.e. bilateral MFGs and ACGs) was calculated on Z-score maps (Tables 1 and 2). Extent of such pixels $>10\%$ in the target gyri was defined as significant cortical neuron loss, and $<10\%$ to $>1\%$ in the target gyri was defined as mild cortical neuron loss, based on a scattering ratio (%) of the normal database.

Results

Areas of cortical neuron loss in the medial frontal lobes were observed bilaterally in all 6 patients with higher brain dysfunction, but not bilaterally in all 12 patients without higher brain dysfunction (Tables 3 and 4). In contrast, areas of cortical neuron loss in the lateral frontal lobes were observed bilaterally in 2 and unilaterally in 3 of 6 patients with higher brain dysfunction, and bilaterally in 1 and unilaterally in 4

Table 3 Summary of 6 patients with higher brain dysfunction and degree of cortical neuron loss in the bilateral frontal lobes and extent (%) of abnormal pixels indicating reduction of benzodiazepine receptor in the bilateral frontal medial cortices

Case No.	Age (yrs)/Sex	Frontal lobe*				Frontal medial cortex (%)			
		Medial		Lateral		MFG		ACG	
		Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt
1	46/F	++	++	++	−	48.0	35.6	9.4	8.3
2	42/F	++	++	++	−	23.9	12.1	18.3	15.6
3	37/F	+	+	+	+	8.9	29.1	0.0	0.0
4	46/F	+	++	−	−	12.1	10.5	1.7	9.4
5	58/F	+	+	+	+	9.1	9.1	0.0	0.0
6	26/F	++	++	+	−	31.6	25.3	21.7	45.6
Mean	age: 42.5 ± 10.7					22.3 ± 15.5	20.3 ± 11.2	8.5 ± 9.6	13.2 ± 17.0

*++: Cortical neuron loss in multiple areas, +: cortical neuron loss in single area, −: no area of cortical neuron loss. ACG: anterior cingulate gyrus, MFG: medial frontal gyrus, yrs: years.

Table 4 Summary of 12 patients without higher brain dysfunction and degree of cortical neuron loss in the bilateral frontal lobes and extent (%) of abnormal pixels indicating reduction of benzodiazepine receptor in the bilateral frontal medial cortices

Case No.	Age (yrs)/Sex	Frontal lobe*				Frontal medial cortex (%)			
		Medial		Lateral		MFG		ACG	
		Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt
7	38/F	−	−	++	−	0.0	1.8	0.0	0.0
8	36/F	−	−	−	−	0.0	0.0	0.0	0.0
9	30/F	−	−	−	++	3.4	4.3	0.0	0.0
10	36/F	−	−	−	−	2.8	4.3	0.0	0.6
11	51/F	−	−	+	−	0.0	2.6	0.0	0.0
12	54/F	−	−	−	−	0.0	0.0	0.0	0.0
13	31/F	−	−	+	+	0.0	0.0	0.0	0.6
14	40/F	−	−	−	−	0.0	0.8	0.0	0.0
15	41/M	−	−	−	−	6.1	0.4	0.6	2.8
16	36/F	−	−	+	−	0.0	0.2	0.0	0.0
17	34/M	−	−	−	−	0.0	3.2	0.0	2.2
18	26/M	−	−	−	−	0.0	0.0	0.0	0.0
Mean	age: 37.8 ± 8.1					1.0 ± 2.0	1.5 ± 1.7	0.1 ± 0.2	0.5 ± 1.0

*++: Cortical neuron loss in multiple areas, +: cortical neuron loss in single area, −: no area of cortical neuron loss. ACG: anterior cingulate gyrus, MFG: medial frontal gyrus, yrs: years.

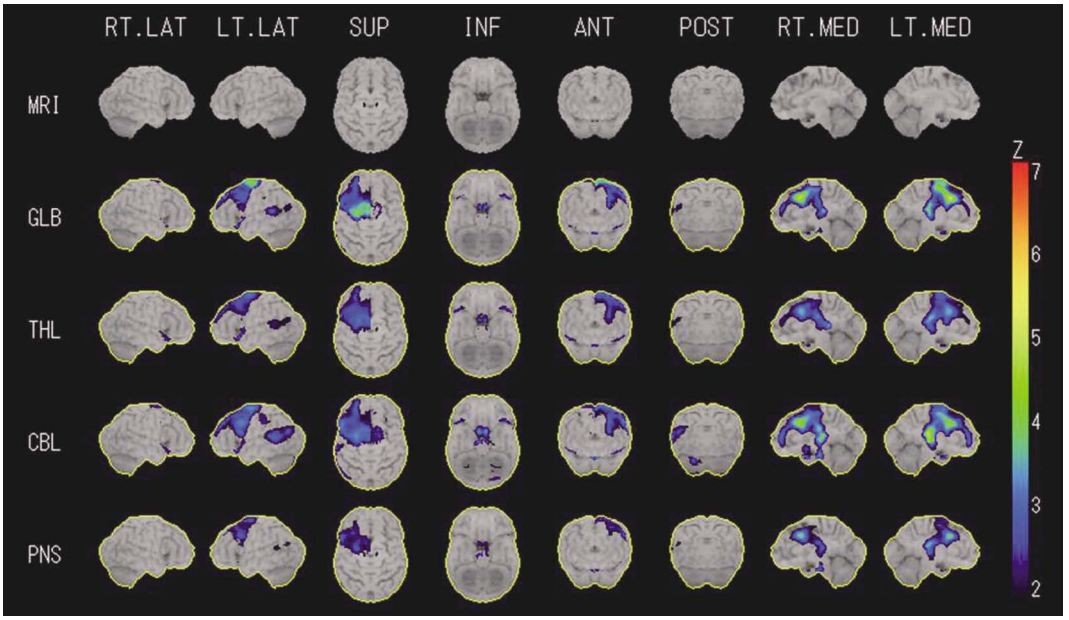


Fig. 1 Group comparison between the normal database and 6 patients with higher brain dysfunction (Z-score >2). *Upper row*: standardized brain surface (8 directions) on magnetic resonance images (MRI), *2nd row*: Z-score images using normalized counts of the global brain (GLB), *3rd row*: Z-score images using normalized counts of the thalamus (THL), *4th row*: Z-score images using normalized counts of the cerebellum (CBL), *5th row*: Z-score images using normalized counts of the pons (PNS). Color in the right bar shows clusters of pixels (Z-score >2). The Z-score images (*2nd row*) show common areas of significant cortical neuron loss in the bilateral medial frontal lobes, especially around the bilateral medial frontal gyri.

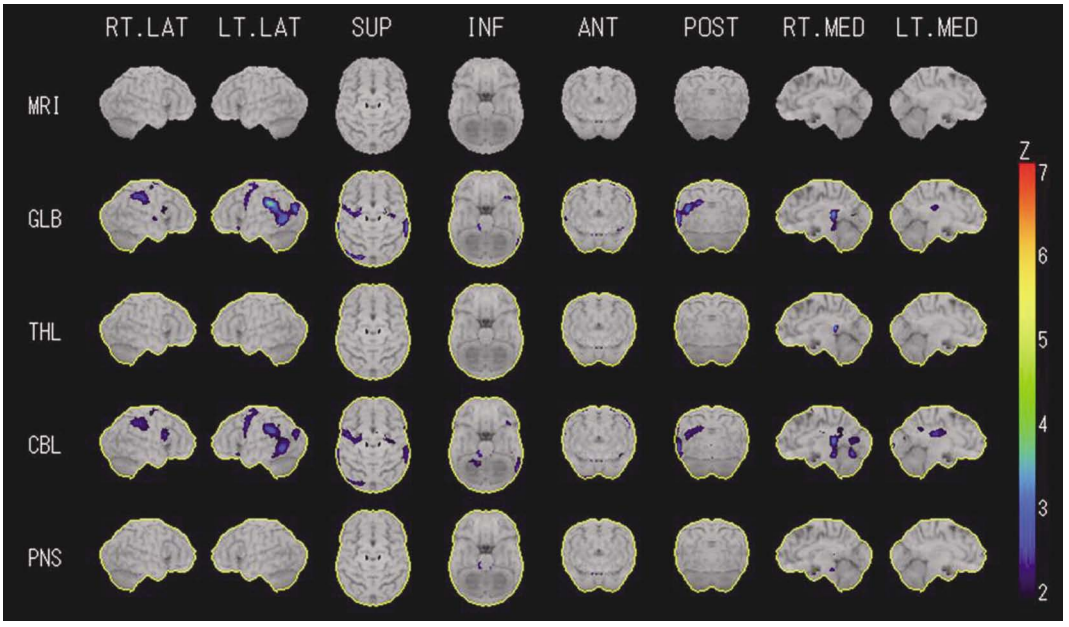
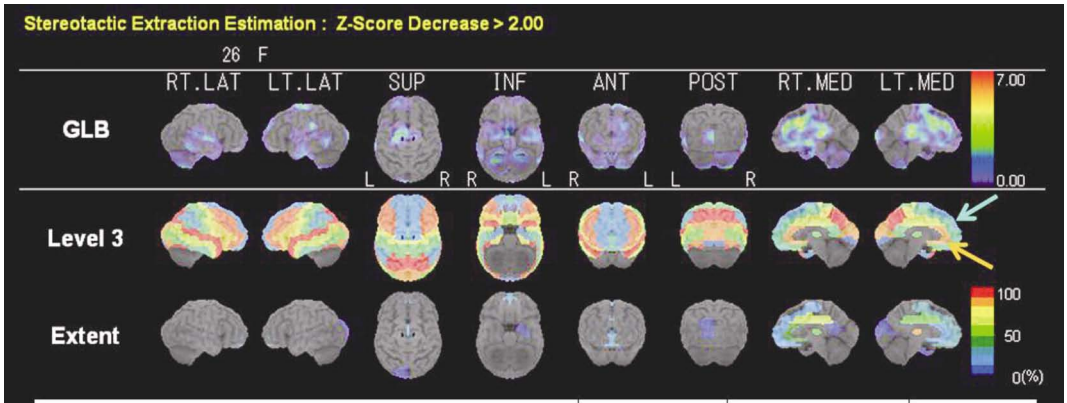


Fig. 2 Group comparison between the normal database and 12 patients without higher brain dysfunction (Z-score >2). *Upper row*: standardized brain surface (8 directions) on magnetic resonance images (MRI), *2nd row*: Z-score images using normalized counts of the global brain (GLB), *3rd row*: Z-score images using normalized counts of the thalamus (THL), *4th row*: Z-score images using normalized counts of the cerebellum (CBL), *5th row*: Z-score images using normalized counts of the pons (PNS). Color in the right bar shows clusters of pixels (Z-score >2). The Z-score images (*2nd row*) show no common areas of significant cortical neuron loss in the bilateral medial frontal lobes.



Extent	>10%	<10%, >1%	0%
MFG: bilateral	4	1	0
: unilateral	1	0	0
ACG: bilateral	2	2	2
: unilateral	2	0	0

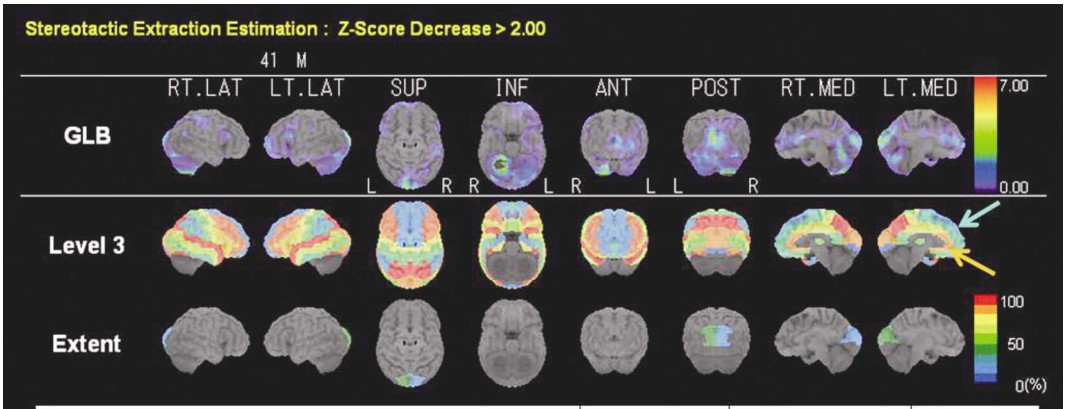
Fig. 3 ***Upper panel*: Stereotactic extraction estimation (SEE) level 3 analysis for the assessment of cortical neuron loss in the bilateral frontal medial cortices. *1st row*: Three-dimensional stereotactic surface projection analysis using normalized counts of global brain (GLM) (Z-score > 0), *2nd row*: each gyrus demonstrated in different colors, *3rd row*: extent (%) of abnormal pixel in each gyrus shown in different colors. *Lower table*: Patients with significant cortical neuron loss in the bilateral and unilateral medial frontal gyri (MFGs) and anterior cingulate gyri (ACGs) summarizing the SEE level 3 analysis. In the 6 patients, significant cortical neuron loss was observed in the bilateral MFGs in 4 patients (67%), unilateral MFG in 1 patient (17%), and bilateral ACGs in 2 patients (33%).**

of 12 patients without higher brain dysfunction (Tables 3 and 4). Group comparison between the normal database and 6 patients with higher brain dysfunction demonstrated common target areas of significant cortical neuron loss in the bilateral medial frontal lobes, especially around the bilateral MFGs (Fig. 1). In contrast, group comparison between the normal database and 12 patients without higher brain dysfunction demonstrated no common target areas of significant cortical neuron loss in the bilateral medial frontal lobes (Fig. 2).

Assessment of significant neuron loss in the bilateral frontal medial cortices was mainly performed in patients with higher brain dysfunction. Significant neuron loss was observed in the bilateral MFGs in 4 patients (67%) and the unilateral MFG in 1 patient (17%), and mild neuron loss was observed in the bilateral MFGs in 1 patient (17%) (Table 3, Fig. 3). Mean extent of abnormal pixels which indicated reduction of BZ receptor was 22.3 ± 15.5% in the left MFG, and 20.3 ± 11.2% in the right MFG (Table 3). Significant cortical neuron loss was observed in the bilateral ACGs in 2 patients (33%), and mild cortical neuron loss was observed in the bilateral ACGs in 2 patients (33%) (Fig. 3). Mean extent of abnormal pixels which indicated reduction of BZ receptor was 8.5 ± 9.6% in the left ACG, and 13.2 ± 17.0% in the right ACG (Table 3). In 6 patients with higher brain dysfunction, significant or mild cortical neuron loss in the bilateral MFGs was more frequent than in the bilateral ACGs (Table 3). In the 12 patients without higher brain dysfunction, mild cortical neuron loss was observed in the bilateral MFGs in 2 patients (17%), unilateral MFG in 4 patients (33%), and unilateral ACG in only 2 patients (17%) (Table 4, Fig. 4).

Discussion

IMZ is a specific radioligand for the central BZ receptor that could be useful to provide a marker of cortical neuron loss after focal cerebral ischemia.[7,17] The reduction of BZ receptor density in reperfused cortex that remained structurally intact is likely to be the result of injury to only a limited number of neurons (i.e., incomplete brain infarction).[4,17] The study of permanent or transient ischemia (lasting 3 to 6 hours) in baboons using [^{18}F]flumazenil as a BZ



Extent	>10%	<10%, >1%	0%
MFG: bilateral	0	2	4
: unilateral	0	4	2
ACG: bilateral	0	0	8
: unilateral	0	2	2

Fig. 4 ***Upper panel*: Stereotactic extraction estimation (SEE) level 3 analysis for the assessment of cortical neuron loss in the bilateral frontal medial cortices. *1st row*: Three-dimensional stereotactic surface projection analysis using normalized counts of global brain (GLM) (Z-score > 0), *2nd row*: each gyrus demonstrated in different colors, *3rd row*: extent (%) of abnormal pixels in each gyrus shown in different colors. *Lower table*: Patients with significant cortical neuron loss in the bilateral and unilateral medial frontal gyri (MFGs) and anterior cingulate gyri (ACGs) summarizing the SEE level 3 analysis. In the 12 patients, no significant cortical neuron loss was observed in the bilateral MFGs or ACGs, and mild cortical neuron loss was observed in the bilateral MFGs in 2 patients (17%), unilateral MFG in 4 patients (33%), and unilateral ACG in only 2 patients (17%).**

receptor ligand and positron emission tomography (PET)[20] has a more direct relevance to study incomplete brain infarction in reperfused cortex using IMZ-SPECT. The study observed decreased BZ receptor binding not only in the infarcted area (to a great degree) but also in the CT-intact opercular cortex overlying the hypodense area (to a lesser degree). Selective neuronal necrosis with sparing of glia and microvessels is seen after transient occlusion of the middle cerebral artery in macaque monkey and rats.[3,5] The extent of ischemic neuronal damage depends on both the magnitude and duration of cerebral ischemia. In another study, up to 60 minutes of middle cerebral artery occlusion followed by 7 days of survival in rats resulted in neuronal necrosis that involved isolated groups of cortical neurons (i.e., incomplete brain infarction), but no cases of cortical infarction.[6] A close correlation existed between the number of necrotic neurons and the severity of the neurological deficits. Incomplete brain infarction defined by the reduction of central BZ receptor density using IMZ-SPECT had been observed within ischemic penumbra salvaged by restored cerebral blood flow in acute stroke,[4] and could occur within hemodynamic cerebral ischemia such as misery perfusion in chronic stroke.[15]

In the present study, the relationship between long-term mild hemodynamic ischemia and the occurrence of incomplete brain infarction in the bilateral medial frontal lobes was estimated by IMZ-SPECT in patients with adult moyamoya disease to establish confirmatory diagnosis of higher brain dysfunction. Our study observed significant cortical neuron loss in the bilateral medial frontal lobes involving MFG and/or ACG in 6 patients with higher brain dysfunction defined by neuropsychological tests (Table 3). Group comparison between 6 patients with higher brain dysfunction and the normal database found significant cortical neuron loss in the bilateral medial frontal lobes involving MFG (Fig. 1). On the other hand, none of the 12 patients without higher brain dysfunctions had significant cortical neuron loss in the bilateral medial frontal lobes involving MFG and/or ACG (Table 4). Group comparison between 12 patients without higher brain dysfunction and the normal database found no

significant cortical neuron loss in the bilateral medial frontal lobes (Fig. 2). These findings suggest that incomplete brain infarction due to long-term mild hemodynamic ischemia could occasionally occur in the bilateral medial frontal lobes involving MFG and/or ACG, and may correlate with higher brain dysfunction in patients with adult moyamoya disease. Recently, an IMZ-SPECT study also demonstrated areas of cortical neuron loss in the bilateral medial frontal lobes involving MFG and/or ACG in patients with higher brain dysfunction after mild traumatic brain injury.[16] Cortical neuron loss in the bilateral medial frontal lobes involving MFG and/or ACG could be an essential finding for the confirmatory diagnosis of higher brain dysfunction.

Statistical imaging analysis using 3D-SSP (Z-score maps) for IMZ-SPECT could provide accurate visual information on cortical neuron loss in the medial frontal lobes. Additionally, the SEE method (level 3: gyrus level analysis) could be useful to estimate cortical neuron loss in the target gyri (i.e. bilateral MFGs and ACGs) which correlate with higher brain dysfunction. In the present study, cortical neuron loss in the target gyri was defined by extent (%) of pixels with significant reduction of BZ receptor density $>10\%$ based on a scattering ratio of the normal database, but how the extent (%) of pixels with significant reduction of BZ receptor density within the target gyri correlates with higher brain dysfunction remains unclear. A multicenter study should be performed to confirm the standard criteria for diagnostic imaging of higher brain dysfunction using IMZ-SPECT.

Lastly, some limitations in this pilot study should be emphasized for designing any future study. The first limitation is the study bias on patient selection due to the single center study. The battery of neuropsychological tests and diagnostic criteria for patients with higher brain dysfunction should be standardized. The second limitation is the possibility of improper management of SPECT image data. Independent section for study data management should perform an audit of all data involving SPECT images. The third limitation is the unreliability of statistical group comparison due to the small number of registered patients. The fourth limitation is the insufficiency of standardized criteria for imaging analysis using the SEE method. The fifth limitation is the absence of verification by other functional imaging modality such as PET. These study limitations should be overcome by a large multicenter study.

In conclusion, long-standing mild hemodynamic ischemia in the anterior circulation of patients with adult moyamoya disease could lead to incomplete brain infarction (selective loss of cortical neurons) defined by reduction of central BZ receptor density within the medial frontal lobes. Statistical imaging analysis using 3D-SSP and SEE methods for IMZ-SPECT could demonstrate significant cortical neuron loss in the bilateral frontal medial cortices involving MFG and/or ACG which correlate with higher brain dysfunction in patients with adult moyamoya disease. A multicenter study should be performed to establish confirmatory diagnosis of higher brain dysfunction in patients with adult moyamoya disease using IMZ-SPECT.

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