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Neuronal Loss in the Bilateral Medial Frontal Lobe Revealed by ^{123}I-iomazenil Single-photon Emission Computed Tomography in Patients with Moyamoya Disease: The First Report from Cognitive Dysfunction Survey of Japanese Patients with Moyamoya Disease (COSMO-Japan Study)

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Abstract

Cognitive impairment in adult patients with moyamoya disease (MMD) is sometimes overlooked and can occur in patients with no ischemic or hemorrhagic lesions. Better profiling and reliable diagnostic methods that characterize the group and associate the impairments and pathology of MMD are required in order to deliver appropriate treatments and support. The potential of ^{123}I-iomazenil single-photon emission computed tomography (SPECT) for this issue has been reported in some studies, but the universality of this method remains unclear. A multicenter study of adult patients (aged 18-60 years) with MMD who experienced difficulties in social lives despite normal activities of daily living was implemented to delineate the common characteristics of this group of patients. In this study, iomazenil SPECT, besides patient characteristics, cognitive functions, and conventional imaging, was acquired to examine whether this method is suitable as a universal diagnostic tool. A total of 36 patients from 12 institutes in Japan were included in this study. Domain scores of world health organization quality of life 26 indicated low self-rating in physical health and psychological domains. The percentages of patients who had <85 in each index were 27.8%-33.3% in the WAIS-III and 16.7%-47.2% in the Wechsler Memory Scale-Revised. The group analysis of iomazenil SPECT demonstrated a decreased accumulation in the bilateral medial frontal areas in comparison with the normal control, whereas there were no specific characteristics on conventional imaging in the cohort. Iomazenil SPECT is a possible universal diagnostic method for the extraction of patients with cognitive impairment in MMD.

Keywords: moyamoya disease, cognitive function, iomazenil SPECT

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Introduction

Moyamoya disease (MMD) is accompanied by cerebrovascular events, including transient ischemic attacks, infarction, or intracranial hemorrhage, and causes severe neurological deficits. Bypass surgery is accepted as the standard treatment for alleviating or preventing such events.[1,2] Patients may also have limited opportunities for higher education or are unable to work due to cognitive disturbances. Known affected cognitive domains in MMD include executive function, processing speed, and verbal function. Cognitive disturbances in MMD have been linked to the presence of ischemic or hemorrhagic lesions, but recent studies have suggested its relationship with chronic hemodynamic insufficiency and disturbed white matter integrity.[3-6] Moreover, the relationship between cognitive disturbances and chronic hemodynamic insufficiency may indicate that these disturbances may be amendable. The characteristics of patients with cognitive disturbances from various angles must be delineated because such patients tend to be overlooked. To provide patients with optimal support, objective diagnostic methods must be developed. The universality of the methods should also be demonstrated to make them reliable and to be widely accepted.

^{123}I-iomazenil (IMZ) is a tracer used for single-photon emission tomography (SPECT) to visualize central benzodiazepine receptor distribution.[7] This tracer is thought to be an indicator of neuronal damage, even in normal-appearing brain areas. A previous study using IMZ-SPECT in a single institute demonstrated neuronal damage in the medial frontal lobe in MMD patients with cognitive impairment, suggesting the possible use of IMZ-SPECT for diagnosing patients with cognitive disturbance in MMD.[8] Recent efforts have been made to minimize the interinstitutional differences in SPECT images attributed to different software programs for SPECT reconstruction supplied by different manufacturers and intrinsic differences of the collimator design in each SPECT camera, which caused different background offset levels in the original SPECT data. The QSPECT software package has therefore been developed to compensate for different amounts of penetrating photons causing different image contrasts among the SPECT cameras, besides the application of identical corrections for attenuation and scatter for SPECT systems supplied by different vendors.

Based on these findings, the Cognitive Dysfunction Survey of Japanese Patients with Moyamoya Disease (COSMO-Japan study) was organized by the Japanese Research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya Disease). In this study, the committee intended to establish the standard finding of cognitive disturbance in patients with MMD. Specifically, this study aimed to delineate the specific pattern of structural and vascular findings in patients with MMD who subjectively felt having some problems in social functioning. Additionally, neuronal damage was evaluated using IMZ-SPECT. This study also aimed to evaluate whether IMZ-SPECT with QSPECT software can be utilized in a multicenter setting.

Materials and Methods

The inclusion and exclusion criteria and evaluation methods of the COSMO-Japan study were previously reported.[9] Patients with MMD who experienced difficulties in daily life were prospectively collected from December 2014 to December 2016 at 12 institutes in Japan. The entry was later extended to December 2017 because of the lack of registered patients. The study was approved by the Ethical Review Board of the Kyoto University Graduate School of Medicine (E-1754) and of each participating institute. All the participants provided written informed consent prior to their inclusion in the study.

Patients aged 18-60 years who were diagnosed with MMD or unilateral MMD, with modified Rankin Scale (mRS) of 0-3, and without large intracranial structural lesions extending more than two cortical arteries in neuroradiological studies were included in the study. Those with quasi-MMD and significant neurological disorders unsuitable for neuropsychological testing were excluded. All the diagnosis was made according to the diagnostic criteria made by the research committee on spontaneous occlusion of the circle of Willis (MMD) in Japan.[10] Inclusion of patients with prior bypass surgery was allowed.

The participants of the COSMO-Japan study were evaluated using ^{123}I-iodoamphetamine (IMP)-SPECT, IMZ-SPECT, MRI (T1 structural image, fluid-attenuated inversion recovery [FLAIR] image, T2 weighted image [WI], T2* WI, and time-of-flight magnetic resonance angiography [TOF-MRA]), and neuropsychological assessment batteries, including Wechsler Adult Intelligence Scale Third Edition (WAIS-III), Wechsler Memory Scale-Revised (WMS-R), Frontal Assessment Battery, Wisconsin Card Sorting Test, Stroop Test, Word Fluency Test, Trail Making Test A/B, Beck Depression Inventory-Second Edition, State-Trait Anxiety Inventory, Frontal Systems Behavior Scale, and the World Health Organization Quality of Life Assessment (WHOQOL) 26. Additionally, a self-assessment questionnaire for awareness of cognitive/behavioral difficulties was administered to investigate the subjective symptoms by which the patient experienced difficulties in daily living. All items were answered in a yes/no fashion (Supplemental Table 1).

Among the dataset we have described above, in this report, patient demographics, cognitive functions (major indices of WAIS-III and WMS-R), subjective awareness

(WHOQOL26 and the self-assessment questionnaire for awareness of cognitive/behavioral difficulties), structural MRI findings, and SPECT findings were analyzed to explore robust methods for identifying patients with cognitive impairment in MMD. WHOQOL26 scores are calculated for each domain (Physical health, Psychological, Social relations and Environment; a range of subscores is 4-20[11]). Detailed analyses of neuropsychological tests were not the main focus of this article, and the results of the WAIS-III and WMS-R and WHOQOL26 were discussed to demonstrate the background of the patients.

Two cerebral blood flow (CBF) images were obtained at rest and after the acetazolamide challenge while performing a single session of SPECT imaging during a sequential intravenous injection of ^{123}I-iodoamphetamine.[12] The QSPECT software was used at each institution to reconstruct the sequential images. Quantitative CBF images at rest and after the acetazolamide challenge were also calculated from this software.[12,13] A sophisticated methodology was applied to ensure the quality of SPECT images prior to the clinical examination of patients; accurate corrections for the attenuation, scatter, and penetrating photons;[12,14-16] and equalization of spatial resolution that are intrinsically different among clinical SPEC cameras.[17] As a result of these works, the SPECT images and quantitative CBF values appeared to be reproducible among the SPECT cameras and thus among institutions as demonstrated in multicenter studies.[12]

In conjunction with the MRI findings, the CBF of each vascular territory (i.e., anterior [ACA], middle [MCA], and posterior cerebral arteries [PCA]) was classified into normal perfusion, hypoperfusion, and decreased but matched perfusion in a qualitative manner.

IMZ-SPECT images were also reconstructed using the QSPECT software at each site after confirming the quality of SPECT images. IMZ-SPECT images were sent to the core laboratory for further data analysis. The spatial resolution was first equalized among the SPECT images sent from each institution.[17] The intrinsic spatial resolution for each SPECT system was obtained prior to the clinical study, which referred to the SPECT images obtained for the realistic three-dimensional brain phantom filled with the IMZ solution in the cortex region.[12,17,18] The three-dimensional stereotactic surface projection software (3D-SSP) was then used to highlight significant differences from the normal database obtained from 17 healthy controls. Results were shown as Z-score maps using the SEE method (level 3: gyrus level), as described in a previous report.[8] A Z-score exceeding 2 was defined as a significant difference, and the area with a Z-score greater than 2 was shown over the surface map with color gradation according to the Z-score. We defined neuronal loss as a decrement of benzodiazepine receptor binding potential detected via iomazenil SPECT. We adopted the "extent ratio" (ER) as a surrogate of neuronal loss. The ER of each region of interest (ROI) was calculated as follows:

Table 1 Patient demographics

N = 36		
Age (median, years)		40.5 (20-57)
Sex (Male:Female)		11:25
Onset	Childhood	9
	Adult	24
	Undetermined	3
Initial symptom	Ischemia	22
	Hemorrhage	6
	Headache	5
	Incidental	3
Education	9-11 years	3
	12-15 years	21
	>16 years	10
	Undetermined	2
Revascularization surgery	Unilateral	4
	Bilateral	16
	None	10
Posterior cerebral artery involvement		10

ER = (number of voxels which have the Z-score above a statistical threshold in each ROI)/(whole number of voxels in the ROI)

Z-score = 1.96 was adopted as the threshold for the calculation of the ER.

Statistical analyses of patient demographics and neuropsychological tests were performed using JMP Pro 14.0.0. Fisher's exact test was applied for categorical variables, and the Wilcoxon rank-sum test was applied for numerical variables. Statistical significance was set at $p < 0.05$.

Results

Patient demographics

A total of 36 patients from 12 institutes in Japan were included in this study. The mean age (standard deviation [SD]) was 39.0 (11.0) years, and 25 patients were female. Additionally, 24 patients had adult onset (14 ischemic, five hemorrhagic, four headache presentation, and one incidental), nine patients had childhood onset (six ischemic, one hemorrhagic, one headache presentation, and one incidental), and three patients had undetermined onset. Education history was 9-11 years in three patients (8.3%), 12-15 years in 23 patients (63.9%), and >16 years in nine patients (25.0%), which corresponded to junior high school graduate, high school graduate, and university graduate in the Japanese education system, respectively. PCA involvement was observed in 10 patients (27.8%). Effective revascularization surgery as assessed via TOF-MRA was performed in bilateral hemispheres in 16 patients, left unilateral in two

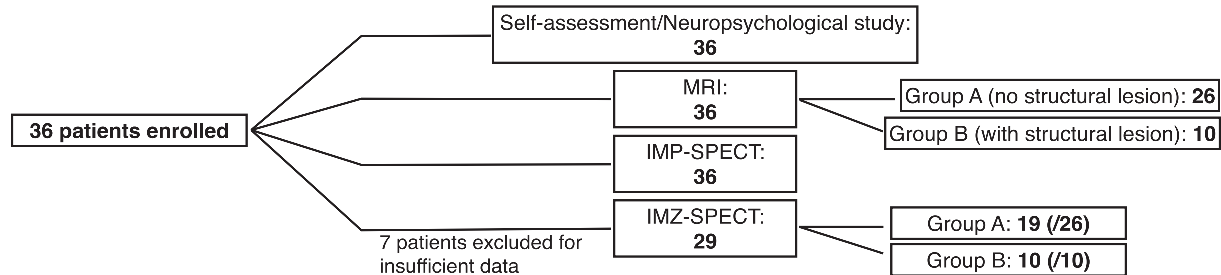

Fig. 1 Study flow chart. MRI, magnetic resonance imaging; IMP, iodoamphetamine; IMZ, iomazenil

patients, and right unilateral in two patients (Table 1).

We conducted an additional MRI committee after the enrollment was closed because many patients had large structural lesions that might influence the result of IMZ-SPECT. Fig. 1 shows the flow chart for the patient grouping. After strictly applying the definition of the large intracranial structural lesion, that is, structural lesions extending more than two cortical arteries, either cortical or subcortical, in neuroradiological studies, 10 patients were discriminated from patients with minimal or no structural lesions (Group B, see below). One patient with right chronic subdural hematoma (Patient 16) and one doubtful diagnosis of MMD on TOF-MRA (Patient 4) were also included in this group (Group B). Another 26 patients without large structural lesions were included in Group A. This grouping was used for the subgroup analysis.

Neuropsychological tests and self-assessment questionnaire

The mean scores of all indices in the WAIS-III and WMS-R were 86.4-94.0. The percentages of patients who had <85 in each index were 27.8%-33.3% for WAIS-III and 16.7%-47.2% for WMS-R (Table 2). The mean domain scores (SD) of WHOQOL26 were 13.8 (3.4) in the physical health domain, 13.0 (3.3) in the psychological domain, 13.8 (3.9) in the social relations domain, and 14.1 (3.4) in the environment domain (Supplemental Table 2). In the self-assessment questionnaire for awareness of cognitive/behavioral difficulties, the rate of patients who answered that they had trouble in daily life exceeded 50% for attention and executive function (Supplemental Table 3).

Magnetic resonance imaging

Fig. 2 shows the findings of the structural MRI of the patients classified as Group B. This group comprised three patients with diffuse ischemic changes in the white matter of the right hemisphere, two patients with diffuse ischemic changes in the white matter of the left hemisphere, one patient with diffuse ischemic changes in the bilateral white matter, and two patients with multiple cortical lesions in the right hemisphere. There was no significant difference between Groups A and B in each index score of WAIS-III or WMS-R, domain score of WHOQOL26, and percentage

Table 2 Results of WAIS-III and WMS-R

		Mean (SD)	Number of patients with score < 85 (%)
WAIS-III	Full-scale IQ	88.4 (16.9)	10 (27.8)
	Verbal IQ	90.8 (18.5)	12 (33.3)
	Performance IQ	87.5 (15.3)	11 (30.6)
	Verbal comprehension	91.6 (17.0)	12 (33.3)
	Perceptual organization	90.2 (15.4)	12 (33.3)
	Working memory	87.3 (17.3)	12 (33.3)
	Processing speed	86.4 (14.4)	11 (30.6)
WMS-R	Verbal memory	88.3 (20.1)	17 (47.2)
	Visual memory	94.0 (17.6)	6 (16.7)
	General memory	87.4 (20.5)	14 (38.9)
	Attention	93.2 (17.2)	10 (27.8)
	Delayed recall	87.5 (20.1)	16 (44.4)

WAIS-III, Wechsler Adult Intelligence Scale Third Edition; WMS-R, Wechsler Memory Scale-Revised; IQ, intelligent quotient; SD, standard deviation

of patients in the self-assessment questionnaire for awareness of cognitive/behavioral difficulties. According to TOF-MRA, 28 patients were diagnosed with bilateral MMD, four with left unilateral MMD, and four with right unilateral MMD. PCA involvement was found in six (23.1%) patients in Group A and four (40%) patients in Group B (p = 0.4129).

IMP-SPECT

A total of 17.6% of all vascular territories were diagnosed with hypoperfusion, and 6.5% of the overall areas were diagnosed as having decreased but matched perfusion. No territories indicated reduced CBF of >20% in reference to the ipsilateral cerebellar hemisphere, except for the territories that were diagnosed as having matched perfusion in Group B. There was no tendency for the localization of hypoperfusion. In Group A, the patients diagnosed with hypoperfusion in each area were nine (36%) in the left MCA territory, seven (28%) in the right MCA territory, eight (32%) in the left ACA territory, and seven (28%) in

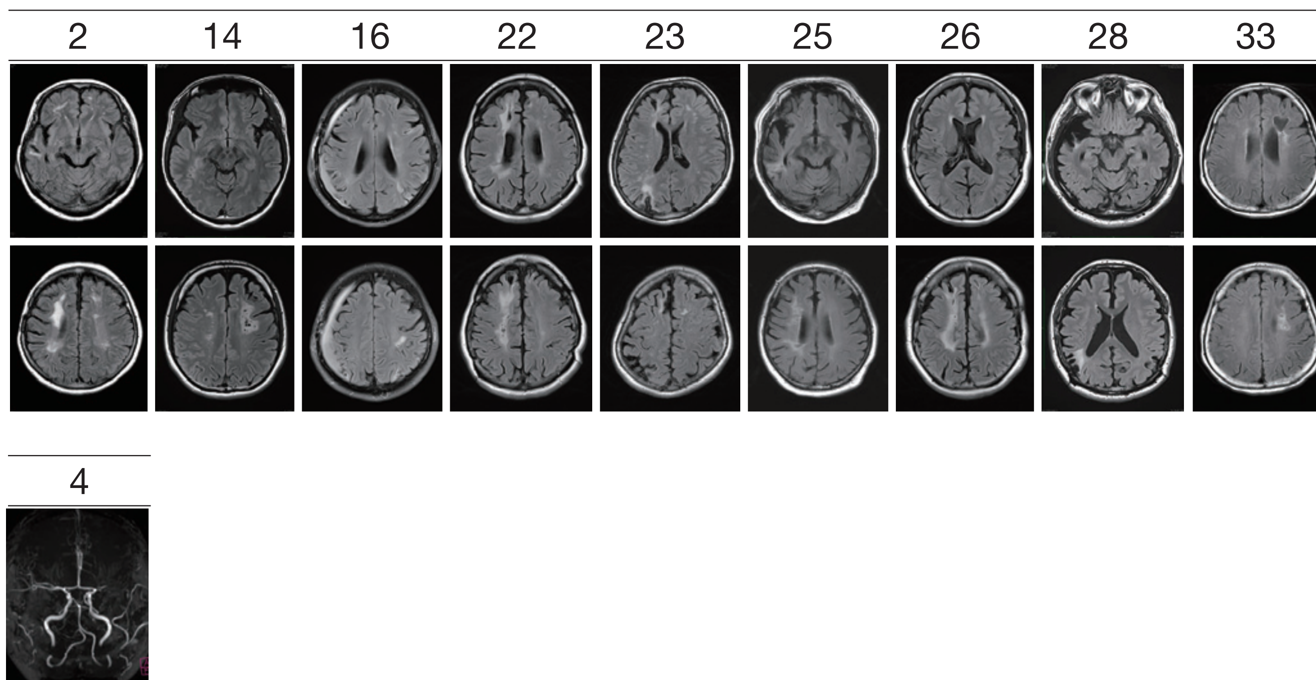

Fig. 2 Findings of magnetic resonance images of Group B. Two slices of fluid-attenuated inversion recovery (FLAIR) images demonstrating the main findings of each patient. Time-of-flight magnetic resonance imaging of Patient 4 without any structural lesion but her vascular involvement not typical for moyamoya disease was displayed in a different row.

right ACA territory. All the patients in Group A were diagnosed as having normal perfusion in bilateral PCA territories.

IMZ-SPECT

We excluded data from seven patients because they were insufficient for the QSPECT analysis. Thus, a dataset of 29 patients was used for further analysis. Overall analysis revealed a significant decrease in iomazenil uptake in the bilateral medial frontal, bilateral perisylvian, and left temporo-occipital areas using normalized counts of the global brain. Subgroup analysis confirmed almost the same result in both Groups A and B. Decreased iomazenil uptake was observed in the bilateral medial frontal, bilateral opercular, and left temporo-occipital areas in Group A and bilateral perisylvian, bilateral medial frontal extending to bilateral medial parietal, right Rolandic, and right temporo-occipital areas in Group B (Fig. 3). The ERs exceeded 50% in bilateral paracentral lobule (55.4% on the left side and 52.5% on the right side), left superior occipital gyrus (100%), bilateral cingulate gyri (74.4% and 73.3%), and bilateral parahippocampal gyri (83.7% and 77.6%) in overall analysis (Supplemental Table 4). The subgroup analysis was available in bilateral (24 patients) and right unilateral (three patients) MMD groups. ERs in the cingulate gyrus of the left and the right side were 77.5% and 76.0% in the bilateral group and 48.8% and 36.8% in the right unilateral group. We could not obtain the ER of the left unilateral group (two patients) because the 3D-SSP program could not manage a group of fewer than three patients.

Discussion

In summary, the standardization of image reconstruction procedures and the equalization of individual differences in spatial resolution among SPECT systems enabled confirmation of the universality of the bilateral medial frontal neuronal loss in patients with MMD who have moderate or mild cognitive impairments in a multicenter study, whereas very few indices of conventional imaging or CBF studies were related to cognitive function. In this cohort, the main subjective complaint was the problem of attention and executive function; scores of WHOQOL26 were low in physical health and psychological domains; no or only mild hemodynamic compromise was noted; and their cognitive function declined beyond SD in at least one dimension in 75% of patients. Structural lesions were observed in 27.8% of patients, whereas there was no significant difference in cognitive or subjective symptoms compared to patients without any significant lesions. None but one patient had a medial frontal structural lesion.

Study population

In this study, we gathered patients who felt or whose physicians in charge were suspected to have trouble in daily life. Consequently, low but within the normal range in mean scores were obtained for all indices of the WAIS-

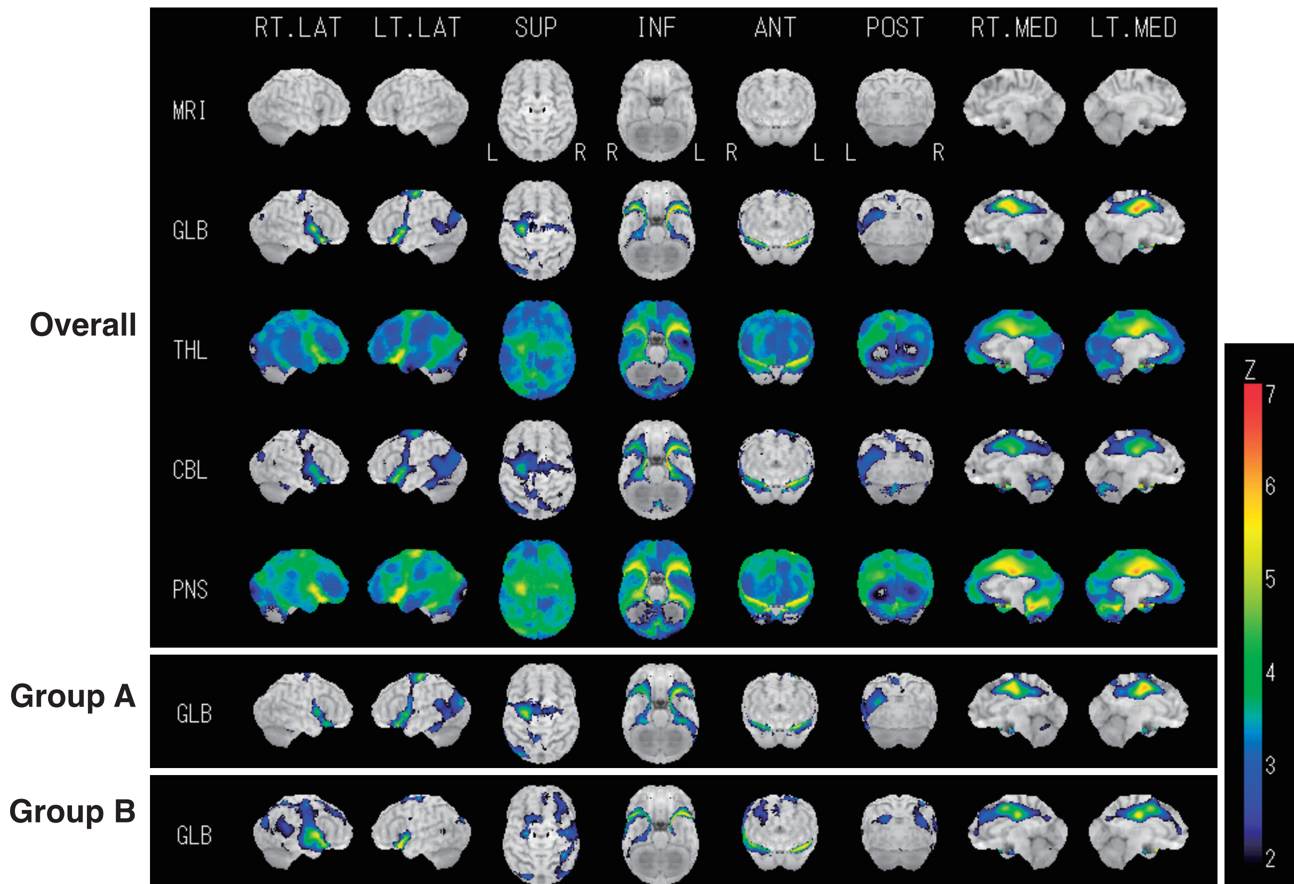

Fig. 3 Group comparison between the normal database and study cohort (Z-score > 2). The upper 8 × 5 matrix indicates the result of the overall analysis (29 patients). Each row demonstrates standardized surface images on magnetic resonance images (MRI), Z-score maps using normalized counts of the global brain (GLB), thalamus (THL), cerebellum (CBL), and pons (PNS). The lower two rows demonstrate the results of the subgroup analysis (Group A: no structural lesion; Group B: with structural lesion on MRI). Z-score maps demonstrate areas of statistically significant decrease of iomazenil uptake in the bilateral medial frontal and perisylvian areas. The findings are similar in overall and subgroup analysis.

III and WMS-R. The education history of the study population was comparable to that of the Japanese population (9-11 years: 16.4%; 12-15 years: 40.4%; >15 years: 30.2%, according to the national census in 2010). Additionally, the rate of patients who were assumed to be within the normal range (i.e., all indices were ≥85) was 25.0% in the WAIS-III or 44.4% in the WMS-R. These results might indicate that patients with severe cognitive impairment were less likely to be included in this study. According to the results of standard neuropsychological tests, the cohort of this study could successfully extract the patient population of MMD who had some difficulty in social functions, such as work and relationships with others, in their daily lives. The domain scores of social relations and environment domains in WHOQOL26 were comparable while those of physical health and psychological domains in this study were lower compared to those of a large Japanese cohort (Supplemental Table 2).[19] The dissociation between social relations/environment and physical health/psychological domains might underlie difficulties in picking up patients with MMD who need support. They may feel satisfied with support from caregivers and the environment although they are unsatisfied physically and psychologically. We believe that the findings of this study may help in approaching such patients from various angles to elucidate the profile of these populations not relying solely on neuropsychological testing, to investigate the optimal diagnostic tool, and to deliver optimal support for these patients. We included patients who were diagnosed as MMD both in their adulthood and childhood because it was difficult to make sure of the true onset of the pathological process of each patient. Whether the ischemic "burden" influence the cognitive function in MMD remains an open question.

Diagnostic imaging and cognitive impairment associated with MMD

Cognitive impairments in patients with MMD have historically been associated with ischemic or hemorrhagic lesions. In the last decade, an association between mild hemodynamic insufficiency without apparent cortical le-

sions and cognitive impairment has been reported. One study of pediatric MMD suggested the effect of PCA involvement on social development.[20] It showed a high rate of PCA involvement in socially unfavorable outcomes (80% vs. 28.3%) and suggested that PCA involvement may lead to a further reduction in CBF even in the anterior circulation because PCA provides significant collateral flow to the anterior circulation. The lower rate of PCA involvement in our study (27.8%) may be associated with the difference in the study cohort; our study included patients with relatively mild symptoms, a normal educational history, a high rate of adult onset, and having jobs. We could not find any remarkable features of this cohort in the location of structural lesions, vascular involvement, or regional hypoperfusion. Sparse findings of these traditional modalities may indicate the difficulty in extracting patients with mild cognitive impairment using conventional diagnostic tools.

IMZ-SPECT as a diagnostic tool for cognitive disturbance of MMD

Previous studies that demonstrated the relationship between cognitive dysfunction in MMD and specific localized changes in neuroimaging were conducted in a single-institute fashion.[8] In this study, the finding of neuronal loss in the medial frontal area on IMZ-SPECT is robust even in a multicenter investigation. For a method to be a diagnostic tool, one must show the universality of the method. We believe this study is the first to demonstrate the robustness of neuroimaging findings concerning cognitive function in patients with MMD in a multicenter fashion despite the intrinsic variation of equipment and data acquisition. Additionally, in our subgroup analysis, reduced uptake of iomazenil was observed in both Groups A and B. This result may also suggest the robustness of this finding and the importance of the integrity of the medial frontal area in pathological changes in MMD.

The executive function and attention are frequently reported to be abnormal in MMD.[4,21,22] Several reports suggested the association of impaired cognitive function in MMD and subtle structural or functional abnormalities in cortical or white matter. Calviere et al. reported in a small group analysis that seven of 13 patients with MMD had executive dysfunction and a possible relationship between executive dysfunction and decreased cerebrovascular reserve in perfusion MRI in the frontal lobe.[3] Additionally, there is increasing evidence of a relationship between frontal white matter integrity and cognitive function. Calviere et al. also showed a correlation between the apparent diffusion coefficient in the frontal white matter and executive dysfunction in patients with MMD. Moreover, a recent study suggested that the mean fractional anisotropy of the lateral prefrontal, cingulate, and inferior parietal areas is related to executive function in patients with MMD.[6] These results suggest the involvement of frontal lobe dysfunction in patients with MMD, especially in the medial area. The neuronal loss revealed as decreased iomazenil uptake in the medial frontal areas in our study may be consistent with these findings. Furthermore, the lateralization of the ER of cingulate gyri in the unilateral MMD group may indicate the impact of chronic hemodynamic insufficiency although the decrement of IMZ uptake was significant even on the uninvolved side.

Notably, our cohort is quite limited such that our findings merely reflect the tendency of the entire MMD cohort, not only patients with cognitive disturbances.

Limitation

This is a small, cross-sectional study of a highly selected cohort among the population with MMD. The number of participants was small, which may reflect the unawareness of cognitive deficits both in patients and medical staff. In this study, we defined neuronal loss as a decrement in iomazenil uptake. Recent reports demonstrated recovery of iomazenil uptake after the modification of CBF.[23,24] It remains to be solved whether the decrement of iomazenil uptake is amenable and whether such intervention can affect cognitive function. The findings on IMZ-SPECT are possibly not characteristic of patients with MMD with cognitive decline but of the patients with MMD in general, although it seems unlikely according to a previous study that assesses IMZ-SPECT results of a smaller group of patients with or without cognitive impairment.[8] Additionally, seven patients were excluded from the analysis of IMZ-SPECT because of insufficient data for analysis. The missing data may affect the reliability of the results. The most important limitation is that the results of IMZ-SPECT were analyzed via comparison with a group with a normal database. Consequently, we could not analyze the relationship between the extent of decreased iomazenil uptake and several indices such as CBF, neuropsychometry, and disease duration. The application of 3D-SSP to a single patient (single patient vs. normal database) is an issue to be addressed in another study.

Conclusions

The characteristics of functional imaging of patients with MMD who have trouble in daily social life were evaluated in a multicenter study. IMZ-SPECT may be a robust diagnostic method for describing neuronal loss in the bilateral medial frontal areas. More studies are required to establish a method for diagnosing cognitive impairments and their relationship with MMD objectively, to properly support patients with such impairments.

Supplementary Material

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Acknowledgments

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Shiho Ubukata deceased August 22, 2022.

Conflicts of Interest Disclosure

The authors have no conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

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