Cognitive Dysfunction Survey of the Japanese Patients with Moyamoya Disease (COSMO-JAPAN Study): Study Protocol

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Abstract

Moyamoya disease is a cerebrovascular occlusive disease characterized by progressive stenosis or by occlusion at the terminal portion of the bilateral internal carotid arteries. The unusual vascular network (moyamoya vessels) at the base of the brain with this disease as collateral channels is developed in this disease. Social independence because of cognitive impairment has recently been recognized as an important unsolved social issue with adult moyamoya disease. The patients with cognitive impairment have difficulty in proving their status because the standard neuroradiological and neuropsychological methods to define cognitive impairment with moyamoya disease are not determined. These patients with cognitive impairment should be supported by social welfare as psychologically handicapped persons. Thus Cognitive Dysfunction Survey of the Japanese Patients with Moyamoya Disease (COSMO-JAPAN study) is planned. In this study, we want to establish a standard finding of the cognitive impairment in patients with moyamoya disease.

Key words: moyamoya disease, cognitive dysfunction, [¹²³I]iomazenil-single photon emission computed tomography, neuropsychological study

Introduction

Moyamoya disease is a cerebrovascular occlusive disease characterized by progressive stenosis or by occlusion at the distal ends of bilateral internal carotid arteries.¹⁾ The unusual vascular network (moyamoya vessels) at the base of the brain of individuals with this disease is considered to represent collateral channels formed as a result of progressive brain ischemic changes.^{1–3)} The etiology of the disease is undefined. The findings that the incidence of the disease is highest in East Asian people and that the condition is frequently familial, suggest the involvement of a genetic factor in its pathogenesis.¹⁾ Extracranial-intracranial bypass surgery has been established as an effective neurosurgical intervention that increases cerebral blood flow (CBF) and prevents from ischemic attacks.^{4,5)} However, difficulty with social independence accompanied by cognitive impairment has recently been recognized as an important unsolved social issue faced by patients with adult moyamoya disease.^{6–8)} These patients are physically independent in daily life, but economi-

cally dependent. It is very difficult for them to obtain vocational skills because of cognitive impairment. These patients with cognitive impairment should be supported by social welfare as psychologically handicapped persons. They have difficulty in proving their status because the standard neuroradiological and neuropsychological methods to define cognitive impairment with moyamoya disease are not determined. Generally, cognitive impairment has been described as a neuropsychological disorder occurring after strokes that shows as disturbances in memory, attention, performance, and social behavioral disturbances mainly in pediatric cases.^{9,10)} However, recent reports have focused on adult cases with neurocognitive impairment even without neuroradiological evidence of major stroke.^{8,11,12)} Nakagawara et al.⁸⁾ indicated that even if infarction has not yet occurred, brain dysfunction was associated with persistent hemodynamic compromise in the medial frontal lobes that can be visualized using [¹²³I]iomazenil (IMZ)-single photon emission computed tomography (SPECT). This technique has the potential to become a tool for diagnosing cognitive impairment in adult moyamoya patients who do not show major abnormalities on computed

tomography (CT) scans or magnetic resonance imaging (MRI). In addition, a common methodology for neuropsychological evaluation of these patients is yet to be determined.^{6,12,13)} In this study, we want to establish the standard finding of the cognitive impairment in patients with moyamoya disease.

Materials and Methods

I. Methods/design

This is a prospective multicenter trial planning to analyze 60 patients with moyamoya disease. The study was approved by the Regional Ethical Review Board at Kyoto University (reference number: E-1754), and all patients will provide written informed consent before inclusion in the trial.

II. Inclusion and exclusion criteria

Inclusion criteria are as follows:

1. Male or female aged above 18 years under 60 years
2. Diagnosed as moyamoya disease or unilateral moyamoya disease on assessment by the neuro-radiological committee¹⁴⁾
3. Without intracranial hemorrhage including intracerebral hemorrhage, intraventricular hemorrhage, and subarachnoid hemorrhage
4. Without a large structural lesions (less than 1 cortical artery region) on neuroradiological studies
5. No neurological disorder influencing neuropsychological assessment, e.g., aphasia, hemianopsia, and agnosia
6. Modified Rankin scale ranging from 0 to 3
7. Without serious cognitive dysfunction assessed by subjective, objective symptoms, or daily life situation
8. Confirmation of informed consent

Exclusion criteria are as follows:

1. Quasi-moyamoya disease
2. Impossible to perform MRI
3. Assessment as unsuitable for this study

These criteria are also described in Table 1.

III. Background data

As background data of the patients, including in this study institute, sex, age, history of education, history of jobs, familial history, reason for diagnosis, modified Rankin scale, medication, and neurological deficits are recorded. In addition, blood sample is collected.

IV. SPECT

Brain N-isopropyl-p-¹²³I-iodoamphetamine (¹²³I-IMP) SPECT using QSPECT/dual table autoradiographic

Table 1 Inclusion and exclusion criteria

Inclusion criteria
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MRI: magnetic resonance imaging.

(ARG) method with three-dimensional stereotactic surface projection (3D-SSP) is performed to calculate the regional cerebral blood flow. To assess the regional cerebral vascular reserve, Diamox challenge SPECT is performed. The procedure for QSPECT/dual table ARG is described elsewhere in more detail.^{15,16)} The data is analyzed by the SEE-JET (stereotactic extraction estimation based on the Japan EC-IC bypass trial study) program.¹⁷⁾

¹²³I-IMZ-SPECT using QSPECT method with 3D-SSP is performed to assess cortical neuronal loss. Cortical neuron loss is analyzed using the SEE method (level 3: gyrus level) for 3D-SSP Z-score maps as previously reported.⁸⁾

V. MRI

MRI scans are also performed in all subjects. The scans are acquired on a 1.5 T or a 3 T scanner using a three-dimensional (3D) sagittal magnetization-prepared rapid gradient-echo imaging sequence, which is specially adjusted for the Japanese Alzheimer's disease Neuroimaging Initiative (J-ADNI) 1/2 protocols. T₁ structural sequences [3D MPRAGE on Siemens (Erlangen, Germany) and Philips Healthcare (Best, the Netherlands), 3D IR-SPGR on GE], FLAIR, T₂WI (Dual Echo), T₂*WI and TOF-MRA images are obtained in this study.¹⁸⁾

VI. Neuropsychological assessment

Basic cognitive ability is evaluated using the

Table 2 Neuroradiological and neuropsychological study

Neuroradiological study
SPECT
¹²³ I-IMP SPECT
¹²³ I-IMZ-SPECT
MRI
MPRAGE/IR-SPGR
FLAIR
T ₂ WI (Dual Echo)
T ₂ *WI
TOF-MRA
Neuropsychological study
WAIS-III
WMS-R
FAB
WCST
Stroop test
Word-fluency
TMT A/B
BDI II
STAI
FrSBe
WHOQOL26

Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) to assess intelligence, the Wechsler Memory Scale-Revised (WMS-R) to assess memory,^{19,20)} and supplemental subtests for each task. Several frontal-functioning tests are also administered to detect specific neuropsychological deficits associated with adult moyamoya disease that co-occurs with difficulty in social independence. The Frontal Assessment Battery (FAB) tests general frontal cognitive ability. The Trail Making Test Part A (TMT-A) assesses speed of information processing,^{21,22)} and the Trail Making Test Part B (TMT-B) and the Wisconsin Card Sorting Test (WCST) assess executive ability.^{5,18)} Stroop test, Word-fluency test, and Frontal Systems Behavior Scale (FrSBe) are also used for frontal lobe function.^{22–24)} The Beck Depression Inventory—Second Edition (BDI II) and State-Trait Anxiety Inventory (STAI) assess depressive state.^{26,27)} In addition, WHOQOL26 assesses the quality of life. The item of neuroradiological and neuropsychological study is summarized in Table 2.²⁸⁾

Discussion

Patients with moyamoya disease often suffer higher cognitive impairments such as memory, attention,

and social behavioral disturbances.^{11–13)} Such cognitive impairments may occur in patients with medial frontal lobe damage including the anterior cingulate cortex. However, confirmatory diagnosis of higher cognitive dysfunction in patients with moyamoya disease without obvious brain damages on CT or MRI imaging has not been established and could become a social issue.⁸⁾

In general, higher brain dysfunction associated with adult moyamoya disease could be detected by both neuropsychological findings and obvious medial frontal lobe damage detected by CT or MRI.^{11–13)} In addition, hemodynamic ischemia in this region is analyzed by SPECT at rest and after Diamox challenge.^{15,16)} More recently, loss of frontal cortical neuron could be estimated by functional neuroimaging using SPECT, because central benzodiazepine receptor mapping using ¹²³I-IMZ is available for clinical use.⁸⁾ IMZ is a specific radioactive tracer for the central benzodiazepine receptor that may be useful as a marker of cortical neuron loss. Recent work using IMZ-SPECT has demonstrated the association between cortical neuron loss in bilateral frontal medial cortices and cognitive dysfunction.⁸⁾

Neuropsychological analysis in patients with brain damage played an important role in the history of developing the research of brain function.^{13,19–22,29)} Among brain dysfunction, higher cognitive dysfunction has been underestimated in the neurosurgical field. This dysfunction is often due to frontal lobe dysfunction. An extensive focus on frontal lobe function has not yet been taken by previous research regarding moyamoya disease. CBF and IMZ studies have shown that antero-medial frontal cortices fed by anterior circulation develop blood insufficiencies.^{8,30)} For this reason, several neuropsychological test batteries to evaluate frontal lobe functioning in relation to hemodynamic compromise were employed for our preliminary study. Based on this preliminary study, we developed this study and adopted several tasks to examine the frontal lobe functions.¹¹⁾ To date, this is the first nation-wide survey of patients with moyamoya disease focusing on the neuroradiological and neuropsychological analysis in association with higher cognitive dysfunction. Patients with cognitive impairment should be supported by social welfare as psychologically handicapped persons.

The data obtained from the results of the study will play an important role in clarifying higher cognitive dysfunction in patients with moyamoya disease.

Conflicts of Interest Disclosure

All authors have no conflicts of interest in this manuscript.

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