



# Cognitive Dysfunction in Adults

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## Abstract

Moyamoya disease is an occlusive cerebrovascular disease characterized by stenosis or occlusion at the distal ends of bilateral internal arteries. The unusual vascular network (moyamoya vessels) around the circle of Willis with this disease is considered to represent collateral channels formed as a result of progressive brain ischemia. Recently, difficulty with social independence accompanied by cognitive impairment in adult has been recognized as an important unsolved social issue faced by patients with adult moyamoya disease. Several reports published, but 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. In this chapter, recent reports including our study about cognitive impairment in adult moyamoya disease are summarized.

## Keywords

Moyamoya disease · Cognitive dysfunction · IMZ-SPECT · MRI · Neuropsychological study

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Moyamoya disease is an occlusive cerebrovascular disease characterized by progressive stenosis or occlusion at the distal ends of bilateral internal arteries [1]. The etiology of the disease is not fully undefined. The findings that the incidence of the disease is highest in, but not confined to, Japanese and that the condition is frequently familial suggest the involvement of a genetic factor including *RNF213* in its pathogenesis [1]. The unusual vascular network (moyamoya vessels) around the circle of Willis with this disease is considered to represent collateral channels formed as a result of progressive brain ischemia [1–3]. Extracranial–intracranial bypass surgery with or without indirect procedures has been established as an effective neurosurgical intervention that increases cerebral blood flow (CBF) and cerebral vascular reserve (CVR) prevents from ischemic attacks [4, 5]. However, difficulty with social independence accompanied by cognitive impairment in adults has recently been recognized as an important unsolved social issue faced by patients with adult moyamoya disease [6–8].

In our report, it provides a profile of neurocognitive dysfunction in adult patients with moyamoya disease using structured neuropsychological tasks. A broad range of cognitive functions was disrupted particularly in the patients who had difficulty with social independence. Mean scores of moyamoya patients with cognitive impairment frontal lobe evaluation tasks (Trail Making Test B and Theory of Mind) were significantly lower than healthy patients [9].

These patients with cognitive impairment should be supported by social welfare as psychologically handicapped persons. The characteristics of these patients are physically independent in daily life, but economically dependent. Because it is very difficult for them to obtain vocational skills because of cognitive impairment. But 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 in mainly pediatric cases [10, 11]. However, recent reports have focused on adult cases with neurocognitive impairment even without neuroradiological evidence of major stroke [8, 9, 12]. It is 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 [<sup>123</sup>I]iomazenil (IMZ)-single photon emission CT (SPECT) [8]. In addition, a common methodology for neuropsychological evaluation of these patients is yet to be fully determined [6, 12, 13]. As for Japanese neurosurgeons, we want to establish the standard finding of the cognitive impairment in the patients with moyamoya disease. A prospective multicenter trial is on-going in Japan [14]. Our inclusion criteria are described especially included as follows contents: (1) Without a large structural lesions (less than 1 cortical artery region) on neuroradiological studies. (2) No neurological disorder influencing neuropsychological assessment, e.g. aphasia, hemianopsia, and agnosia. (3) Modified Rankin scale ranging from 0 to 4. Without serious cognitive dysfunction assessed by subjective, objective symptoms or daily life situation [14]. 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 deficit are recorded.

In our study [14], MRI scans were also performed in all subjects. The scans were acquired on a 1.5 T or a 3 T scanner. T1 structural sequences (3D MPRAGE on Siemens and Philips, 3D IR-SPGR on GE), FLAIR, T2WI (Dual Echo), T2\*WI, and TOF-MRA images are obtained in this study [15]. Brain N-isopropyl-p- [<sup>123</sup>I] iodoamphetamine (*123I*-IMP) SPECT using QSPECT/dual-table autoradiographic (ARG) method with three-dimensional stereotactic surface projection (3D-SSP) is performed to calculate regional cerebral blood flow. To assess regional cerebral vascular reserve, Diamox challenge SPECT is performed. <sup>123</sup>I-Iomazenil (IMZ)-SPECT using QSPECT method with 3D-SSP is performed to assess cortical neuronal loss. Cortical neuron loss was analyzed using the stereotactic extraction estimation (SEE) method (level 3: gyrus level) for 3D-SSP Z-score maps as previously reported [8]. These data will clarify the role of neuronal loss and volume of the brain in the cognitive dysfunction of moyamoya disease.

We used the batteries for neuropsychological assessment as follows [14]. Basic cognitive ability was evaluated using the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) to assess intelligence, the Wechsler Memory Scale-Revised (WMS-R) to assess memory [16, 17], and supplemental subtests for each task. Several frontal-functioning tests were 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) tested general frontal cognitive ability. The Trail Making Test Part A (TMT-A) assessed speed of information processing [15, 18] and the Trail Making Test Part B (TMT-B) and the Wisconsin Card Sorting Test assessed executive ability [5]. Word-fluency test and Frontal Systems Behavior Scale (FrSBs) are also used for frontal lobe function [19, 20]. The Beck Depression Inventory—Second Edition (BDI II) and State-Trait Anxiety Inventory (STAI) assess depressive state [21, 22]. In addition, WHOQOL26 assesses quality of life. These batteries are useful to assess neurophysiological functions of moyamoya disease. The item of neuroradiological and neuropsychological study is summarized in Table 11.1. To study the cognitive functions of the patients with moyamoya disease, we emphasize these batteries are important.

This study was named Cognitive Dysfunction Survey of the Japanese Patients with Moyamoya Disease (COSMO Japan study) and the protocol is already published. Inclusion of the patients was already closed, all the data obtained in this study is analyzing now. These data will clear the origin of cognitive impairment in adult moyamoya disease [14].

Illustrative case. 30 year-old, female. MRI (FLAIR) image indicates no major infarction or gross injured area. MRA shows severe stenosis of both internal carotid arteries which is a characteristic of moyamoya disease. She has cognitive dysfunction mainly topographical disorientation. She was dismissed several times by companies (Fig. 11.1).

Patients with moyamoya disease often suffer higher cognitive impairments such as memory, attention, and social behavioral disturbances [9, 12, 13]. However

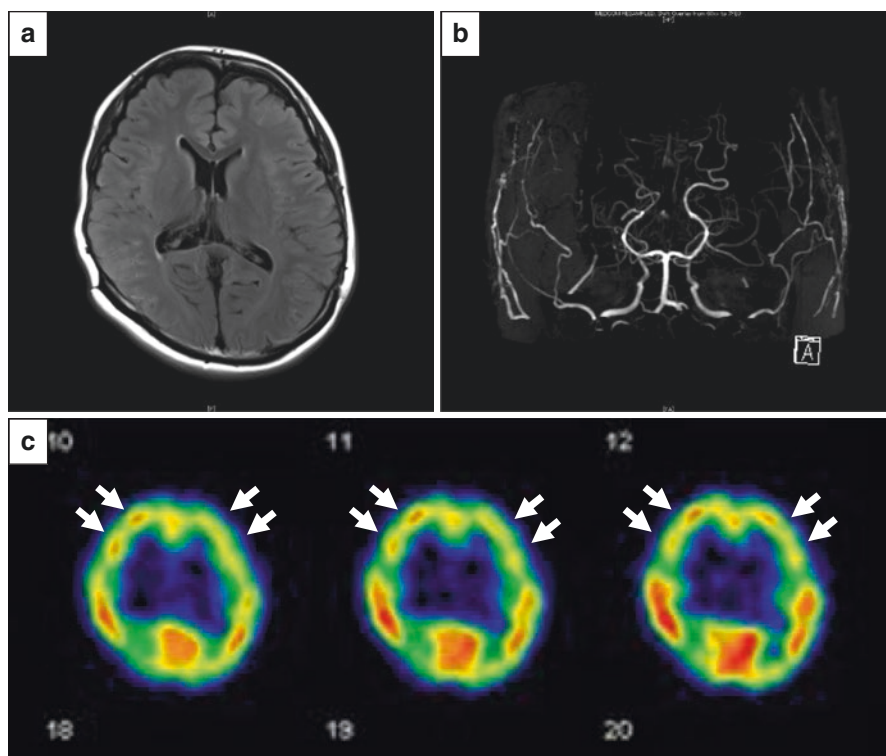
**Table 11.1** Neuroradiological and Neuropsychological studies employed cognitive dysfunction study of moyamoya disease

Neuroradiological study
SPECT
<sup>123</sup> I-IMP SPECT
<sup>123</sup> I-IMZ-SPECT
MRI
MPRAGE/IR-SPGR
FLAIR
T2WI (dual echo)
T2*WI
TOF-MRA
Neuropsychological study
WAIS-III
WMS-R
FAB
WCST
Stroop test
Word fluency
TMT A/B
BDIII
STAI
FrSBe
WHOQOL26

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 social issue [8]. Such cognitive impairments may occur in patients with medial frontal lobe damage including the anterior cingulate cortex.

Karzmark et al. reported that twenty patients (67%) of adult moyamoya disease exhibited small T2 hyperintensities in the cerebral subcortical white matter on brain MRI but no evidence of gray matter damage. Significant cognitive impairment was present in 7 patients (23%). Executive functioning, mental efficiency, and word finding were the ability areas most frequently impaired, whereas memory was relatively intact. Clinically significant emotional distress (depression and/or anxiety) was present in 11 patients (37%). Comparable cognitive findings were also observed in the subset of 10 patients (33%) with completely normal static brain MRI [12].

Kazumata et al. performed neurobehavioral and neuroimaging examinations in 25 adults with MMD prior to and > 12 mo after revascularization surgery. In this study, cognitive function was investigated using the Wechsler Adult Intelligence Scale-III, Trail Making Test, Wisconsin Card Sorting Test, Continuous Performance Test, Stroop test, and Wechsler Memory Scale. They assessed white matter integrity using diffusion tensor imaging, brain morphometry using magnetization-prepared rapid gradient-echo sequences, and brain connectivity using resting-state functional magnetic resonance imaging (MRI). Cognitive examinations revealed significant changes



**Fig. 11.1** 30 y.o. female. (a) MRI (FLAIR) axial image. (b) MRA anterior-posterior view. (c) IMZ-SPECT axial image. Arrows indicated marked low accumulation in both frontal lobes

in the full-scale intelligence quotient (IQ), performance IQ (PIQ), perceptual organization (PO), processing speed, and Stroop test scores after surgery. Enlargement of the lateral ventricle, volume reductions in the corpus callosum and subcortical nuclei, and cortical thinning in the prefrontal cortex were also observed. Fractional anisotropy in the white matter tracts, including the superior longitudinal fasciculus, increased 2 to 4 years after surgery, relative to that observed in the presurgical state. In addition, Resting-state brain connectivity was increased predominantly in the fronto-cerebellar circuit and was positively correlated with improvements in PIQ and PO [23].

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 magnetic resonance (MR) imaging [9, 12, 13]. In addition, hemodynamic compromise in this region is analyzed by SPECT at rest and after Diamox challenge [24, 25]. More recently, loss of frontal cortical neuron could be estimated by functional neuroimaging using SPECT, because central benzodiazepine receptor mapping using [123I]iomazenil (IMZ) is available for clinical use [8]. IMZ is a specific radioactive tracer for the central BZ 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].

Among brain dysfunction, higher cognitive dysfunction has been underestimated in the neurosurgical field. Neuropsychological analysis in the patients with brain damage played an important role in the history of developing the research of brain function [15–18, 24, 26]. 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. Recent CBF and IMZ studies have shown that antero-medial frontal cortices fed by anterior circulation develop blood insufficiencies [8, 27]. For this reason, several neuropsychological test batteries to evaluate frontal lobe functioning in relation with hemodynamic compromise were employed for our preliminary study. Based on this preliminary study, we develop our study and adopt several tasks to examine frontal lobe functions [9]. To date, several surveys of the patients with moyamoya disease focusing neuroradiological and neuropsychological analysis in association with higher cognitive dysfunction were published. The patients with cognitive impairment should be supported by social welfare as psychologically handicapped persons. The results of neurophysiological studies including our study will play an important role in clarifying higher cognitive dysfunction in the patients with moyamoya disease.

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