Long-Term Cognitive Changes after Revascularization Surgery in Adult Patients with Ischemic Moyamoya Disease

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Abstract

Introduction: Revascularization surgery for adult moyamoya disease (MMD) with ischemic presentation changes cognitive function and prevents further cerebral ischemic events. Most studies however repeated neuropsychological evaluation within 1 year after surgery. Our previous prospective cohort study of adult patients with MMD with misery perfusion who underwent direct revascularization surgery showed cognitive improvement and decline in 31% and 44%, respectively, of the patients 2 months after surgery. The present prospective study aimed to elucidate the 5-year cognitive changes after direct revascularization surgery in adult patients with cerebral misery perfusion due to ischemic MMD by following the same patients. Methods: In total, 31 patients were prospectively followed up for 5 years after direct revascularization surgery. Five types of neuropsychological tests were performed preoperatively, 2 months after surgery, and at the end of the 5-year follow-up. Cerebral blood flow (CBF) in the symptomatic cerebral hemisphere relative to that in the ipsilateral cerebellar hemisphere (hemispheric relative CBF [RCBF]) was measured using brain perfusion single-photon emission computed tomography preoperatively and at the end of the 5-year follow-up. Results: Based on results of pre- and postoperative neuropsychological tests, 11, 10, and 10 patients showed cognitive improvement, no change in cognitive function, and cognitive decline, respectively, at the end of the 5-year follow-up. These ratios were not significantly different compared with those 2 months after surgery (cognitive improvement, no change in cognitive function, and cognitive decline in 10, 8, and 13 patients, respectively). Although hemispheric RCBF was significantly greater at the end of the 5-year follow-up than before surgery in patients with cognitive improvement (80.7 ± 6.1% vs. 92.9 ± 5.5%; p = 0.0033) and in those showing no change in cognitive function (85.6 ± 3.5 vs. 91.5 ± 5.2%; p = 0.0093), this value was significantly lower at the end of the 5-year follow-up than before surgery in patients with cognitive decline (83.8 ± 3.7 vs. 81.0 ± 5.8%; p = 0.0367). Conclusion: One-third of adult patients with cerebral misery perfusion due to ischemic MMD who underwent direct revascularization surgery exhibited cognitive improvement, and one-third exhibited decline at the end of the 5-year follow-up. The former and latter patients had increased and de-
Moyamoya disease (MMD) is characterized by chronic bilateral steno-occlusive changes in the terminal portion of the internal carotid artery and abnormal arterial collateral flow at the base of the brain [1, 2]. For adult patients with ischemic symptoms due to MMD, strict medical management alone including an antiplatelet drug such as cilostazol may be recommended when the symptomatic cerebral hemisphere exhibits stable hemodynamics [3–5]. In contrast, when the symptomatic cerebral hemisphere exhibits hemodynamic compromise such as misery perfusion, typical treatment is direct revascularization surgery, such as anastomosis of the superficial temporal artery to the middle cerebral artery, with or without indirect revascularization surgery, such as encephalo-duro-myo-synangiosis [3, 4, 6–10].

Revascularization surgery in adult MMD changes cognitive function and prevents further cerebral ischemic events [6, 11–15]. Most adult MMD patients who undergo revascularization surgery do not show cognitive changes relative to cognitive ability before surgery, although some patients do demonstrate improved or worsened cognitive function postoperatively [16]. We previously carried out a prospective study in which adult patients with ischemic MMD who had misery perfusion in the symptomatic cerebral hemisphere underwent direct revascularization surgery and neuropsychological testing before and after surgery [10]. This study showed that 31% and 44% of the patients had postoperative cognitive improvement and decline, respectively [10]. Immediately after direct revascularization surgery, cerebral hyperperfusion leads to cognitive dysfunction [10]. In contrast, a gradual increase in cerebral blood flow (CBF) in later stages leads to improvements in cognitive function in the absence of early-stage cerebral hyperperfusion [10].

Most of these studies however repeated neuropsychological evaluation within 1 year after surgery [10, 11, 13–16]. Only 1 study performed neuropsychological testing >1 year but <2 years postoperatively [12]. Longer term cognitive changes after revascularization surgery for adult MMD patients remain uninvestigated. The present prospective study aimed to elucidate the 5-year cognitive changes after direct revascularization surgery for adult patients with cerebral misery perfusion due to ischemic MMD by following up previously reported patients [10] for 5 years.

Materials and Methods

Study Design
The present study was originally designed as a prospective observation study [10]. This study was carried out in accordance with the guidelines of the World Medical Association and the Declaration of Helsinki, and the protocol was reviewed and approved by the Iwate Medical University School of Medicine institutional Ethics Committee (approval No. H17-26). All patients provided written, informed consent prior to participating.

Inclusion Criteria of Patients
In total, 36 Japanese patients who visited our department from January 2008 to March 2016 and who met the following inclusion criteria were prospectively included in the original study [10]: (1) the presence of MMD according to the diagnostic criteria of the Research Committee on Spontaneous Occlusion of the Circle of Willis of the Ministry of Health, Labour and Welfare of Japan [2]; (2) age >30 years but <60 years; (3) a modified Rankin disability scale score of 0 or 1; (4) the presence of episodes of carotid territory ischemic symptoms occurring ≤3 months before presentation to our department; (5) the absence of major cerebral infarction on magnetic resonance (MR) imaging; (6) the presence of misery perfusion in the symptomatic cerebral hemispheres on brain 15O gas positron emission tomography. Two patients declined surgery, and the remaining 34 patients underwent direct revascularization surgery. Two of the 34 patients were excluded following development of new ischemic lesions in the cerebral hemisphere ipsilateral to surgery as demonstrated with MR imaging, 1 day after surgery [10]. Thus, 32 patients were finally included in the original study [10].

Assessment of Cognitive Changes
Neuropsychological testing for assessment of cognitive changes was performed as described previously [10]. Briefly, each patient underwent the following neuropsychological tests: the Wechsler Adult Intelligence Scale – Revised (WAIS-R), which measures the verbal and performance intelligence quotient (IQ) [17]; the Wechsler Memory Scale (WMS), which measures the memory quotient (MQ) [18]; and the Rey-Osterrieth Complex Figure test (Rey test), which consists of copying and recalling a complex figure [19]. Cognitive abilities of the patients were thus evaluated according to scores on these 5 tests (WAIS-R verbal IQ, WAIS-R performance IQ, WMS MQ, Rey copy, and Rey recall) [10].

The neuropsychological tests were performed before surgery, 2 months after surgery [10], and at the end of the 5-year follow-up. For each neuropsychological test in each patient, a difference between scores before and after surgery (postoperative value – preoperative value) was calculated and defined as the Δ value. A significant increase was defined as a Δ value >12.4 for WAIS-R verbal IQ, >14.9 for WAIS-R performance IQ, >16.9 for WMS MQ, >2.6 for Rey copy, or >9.9 for Rey recall [20]. A significant decrease was defined as a Δ value <−5.6 for WAIS-R verbal IQ, <−5.1 for WAIS-R performance IQ, <−7.5 for WMS MQ, <−1.8 for Rey copy, or...
< −4.1 for Rey recall [20]. ∆ Values outside these ranges were defined as unchanged [20]. When a patient had a significant increase in one or more neuropsychological tests, the patient was considered to have cognitive improvement [20]. When a patient had a significant decrease in one or more neuropsychological tests, the patient was considered to have cognitive decline [20]. When a patient had unchanged ∆ Values in all 5 neuropsychological tests, the patient was considered to have no change in cognitive function [20]. These determinations of cognitive changes were done 2 months after surgery [10] and at the end of the 5-year follow-up.

Brain Perfusion Single-Photon Emission Computed Tomography

CBF was measured using brain perfusion single-photon emission computed tomography (SPECT) with N-isopropyl-p-[123I]-iodoamphetamine according to methods described previously [10, 21]. Patients underwent brain perfusion SPECT preoperatively, on the 1st postoperative day [10], and at the end of the 5-year follow-up. Postoperative cerebral hyperperfusion was defined as described previously based on brain perfusion SPECT findings before and on the day after surgery [10].

Anatomic standardization of preoperative and the 5-year follow-up SPECT images into the standard brain size and shape was performed using linear and nonlinear transformation with SPM2 [22] so that the brain images obtained from all study participants were anatomically identical. A 3-dimensional stereotaxic region of interest (ROI) template was used to set 318 constant ROIs in the cerebral and cerebellar hemispheres automatically [23]. Then, the ROIs were grouped into 10 segments (callosomarginal, pericallosal, precentral, central, parietal, angular, temporal, and posterior regions) in each hemisphere according to arterial supply, and these 10 segments were combined. The mean radioactive count on the SPECT images was measured in both cerebral and cerebellar hemispheric ROIs, and then, the mean radioactive count in the cerebral ROI in the symptomatic cerebral hemisphere relative to that in the ipsilateral cerebral ROI (hemispheric relative CBF [RCBF]) was calculated for each patient. In addition, for each patient, the difference between hemispheric RCBF before surgery and at the end of the 5-year follow-up (postoperative value − preoperative value) was calculated and defined as Δhemispheric RCBF.

Patient Management during and after Surgery

In all 32 patients, frontal craniotomy in the symptomatic cerebral hemisphere was performed, and the parietal branch of the superficial temporal artery was anastomosed to the M4 portion of the middle cerebral artery in the precentral region on the 3-dimensional stereotaxic ROI template because this region exhibited misery perfusion on preoperative brain 15O gas positron emission tomography [10]. Cerebral hyperperfusion was diagnosed if a patient showed a major focal increase in CBF in the anastomosed area (the precentral region on the surgically treated side) as demonstrated by brain perfusion SPECT images the day after surgery [10]. Cerebral hyperperfusion syndrome was also diagnosed if a patient showed headache, seizures, altered consciousness, and/or new or worsening neurological symptoms, including aphasia, hemiparesis, or dysarthria between 12 h and 30 days postoperatively, in addition to cerebral hyperperfusion on brain perfusion SPECT [10].

Each patient received medical treatments in the outpatient setting: attempts were made to keep systolic blood pressure below 140 mm Hg, hemoglobin A1c below 6.5%, and low-density lipoprotein cholesterol below 140 mg/dL. Patients were urged to not smoke. No antiplatelet drugs were administered. MR angiography was performed before surgery and at the end of the 5-year follow-up to look for formation of collateral flow from direct revascularization.

Statistical Analysis

Data are expressed as the mean ± standard deviation. Differences in percentages of patients with cognitive improvement, no change in cognitive function, and cognitive decline between 2 months after surgery and the end of the 5-year follow-up were evaluated using the Wilcoxon signed-rank test with continuity correction. Changes in hemispheric RCBF between preoperative status and the end of the 5-year follow-up were evaluated using the Wilcoxon signed-rank test. Differences in Δhemispheric RCBF among patients with cognitive improvement, no change in cognitive function, and cognitive decline at the end of the 5-year follow-up were evaluated using Scheffe’s F test. Statistical significance for all analyses was set at p < 0.05.

Results

During the 5-year follow-up period, one of the 32 patients withdrew from the present study. All of the remaining 31 patients completed neuropsychological testing and brain perfusion SPECT at the end of the 5-year follow-up.

During the 5-year follow-up, no patients experienced further ischemic events or new hemorrhagic events. Formation of collateral flow from direct revascularization was identified in all 31 patients when MR angiograms were compared before surgery and at the end of the 5-year follow-up. These comparisons of MR angiograms also showed no morphological changes in the vertebobasilar arteries at the end of the 5-year follow-up.

Of the 31 patients analyzed, 10, 8, and 13 patients were determined to have cognitive improvement, no change in cognitive function, and cognitive decline, respectively, 2 months after surgery [10]. Figure 1 shows chronological changes in each neuropsychological test score in the 10 patients with cognitive improvement 2 months after surgery and the end of the 5-year follow-up. But two other patients had a new, significant increase at the end of the 5-year follow-up. For ΔWAIS-R verbal IQ, 2 of 6 patients with a significant increase 2 months after surgery exhibited no change, but two other patients had a new, significant increase at the end of the 5-year follow-up. For ΔWAIS-R performance IQ and ΔRey recall, 1 patient had a new, significant increase at the end of the 5-year follow-up. For ΔWMS MQ, 1 of 2 patients with a significant increase 2 months after surgery exhibited no change, but 3 other patients had a new, significant increase at the end of the 5-year follow-up. Therefore, of 10 patients with cognitive improvement 2
months after surgery, one exhibited no change in cognitive function, and 9 retained cognitive improvement at the end of the 5-year follow-up.

Figure 2 shows chronological changes in each neuropsychological test in the 8 patients without a change in cognitive function 2 months after surgery. For ∆WAIS-R verbal IQ and ∆Rey recall, 1 patient had a new, significant increase at the end of the 5-year follow-up. For ∆WAIS-R performance IQ, ∆WMS MQ, and ∆Rey copy, all 8 patients remained unchanged at the end of the 5-year follow-up. Therefore, of 8 patients without a change in cognitive function 2 months after surgery, 2 exhibited cognitive improvement, and 6 remained cognitively unchanged at the end of the 5-year follow-up.

Figure 3 shows chronological changes in each neuropsychological test score in 13 patients with cognitive decline 2 months after surgery. For ∆WAIS-R verbal IQ, 4 of 7 patients with a significant decrease 2 months after surgery exhibited no change, but another patient had a new, significant decrease at the end of the 5-year follow-up. For ∆WAIS-R performance IQ, 1 of 6 patients with a significant decrease 2 months after surgery exhibited no change. For ∆WMS MQ, 1 patient with a significant decrease 2 months after surgery exhibited no change, but 2 other patients had a new, significant decrease at the end of the 5-year follow-up. For ∆Rey copy, 2 patients had a new, significant decrease at the end of the 5-year follow-up. For ∆Rey recall, 1 patient with a significant decrease 2 months after surgery exhibited no change at the end of the 5-year follow-up. Therefore, of 13 patients with cognitive decline 2 months after surgery, 3 exhibited no change in cognitive function, and 10 continued to show cognitive impairment at the end of the 5-year follow-up. Seven of 9 patients with cerebral hyperperfusion syn-
drome after surgery continued to show cognitive impair-
ment even at the end of the 5-year follow-up. Three other 
patients with cognitive decline at the end of the 5-year 
follow-up had asymptomatic cerebral hyperperfusion on 
brain perfusion SPECT on the day after surgery.

Based on the above results, 11, 10, and 10 patients were 
considered to have cognitive improvement, no change in 
cognitive function, and cognitive decline, respectively, at 
the end of the 5-year follow-up. These ratios were not sig-
ificantly different compared with those 2 months after 
surgery.

Figure 4 shows changes in hemispheric RCBF in pa-
tients with cognitive improvement, no change in cogni-
tive function, and cognitive decline at the end of the 
5-year follow-up. The hemispheric RCBF was signifi-
cantly greater at the end of the 5-year follow-up than before 
surgery in patients with cognitive improvement (80.7 ± 
6.1% vs. 92.9 ± 5.5%; \( p = 0.0033 \)) or no change in cogni-
tive function (85.6 ± 3.5 vs. 91.5 ± 5.2%; \( p = 0.0093 \)). This 
value was significantly lower at the end of the 5-year fol-
low-up than before surgery in patients with cognitive de-
cline (83.8 ± 3.7 vs. 81.0 ± 5.8%; \( p = 0.0367 \)). ∆Hemisph-
eric RCBF differed significantly among these 3 patient 
groups (cognitive improvement vs. no change in cogni-
tive function, \( p = 0.0019 \); no change in cognitive function 
vs. cognitive decline, \( p < 0.0001 \); and cognitive decline vs. 
cognitive improvement, \( p < 0.0001 \)) and was, in the order 
of descending prevalence, cognitive improvement (12.1 ± 
3.1), no change in cognitive function (5.9 ± 4.3), and cogni-
tive decline (−2.8 ± 3.5). Figures 5 and 6 show MR an-
giograms and brain perfusion SPECT images in a patient 
with cognitive improvement and in a patient with cogni-
tive decline at the end of the 5-year follow-up, respective-
ly.
Discussion

The present prospective study demonstrated that one-third of adult patients with cerebral misery perfusion due to ischemic MMD who underwent direct revascularization surgery exhibited cognitive improvement, and one-third had cognitive decline at the end of the 5-year follow-up. The results also indicated that the former and latter patients had increased and decreased CBF, respectively, in the affected cerebral hemisphere at the end of the follow-up period.

Fig. 3. Chronological changes in Δ value of each neuropsychological test score in 13 patients with cognitive decline 2 months after surgery. Upper and lower dotted lines indicate cutoff points of a significant increase and decrease, respectively, for each neuropsychological test score.

Fig. 4. Changes in hemispheric RCBF in patients with cognitive improvement, no change in cognitive function, and cognitive decline at the end of the 5-year follow-up.
Several retrospective studies reported the incidence of further ischemic or new hemorrhagic events after direct revascularization surgery in adult patients with ischemic MMD: 8% for 56.2 months [24], 0% for 38.2 months [25], and <0.2% for 60 months [26]. Our results showing no further ischemic events or new hemorrhagic events during the 5-year follow-up were comparable with these previous findings.

In the present study, cognitive function in 6 patients changed at the end of the 5-year follow-up compared with that of 2 months after surgery. However, the percentages of patients with cognitive improvement, no change in cognitive function, and cognitive decline did not change, and one-third of adult patients with cerebral misery perfusion due to ischemic MMD who underwent direct revascularization surgery exhibited cognitive improvement, and one-third had cognitive decline over the long term. In particular, most patients with cerebral hyperperfusion syndrome after surgery continued to show cognitive dysfunction even at the end of the 5-year follow-up. A case of an adult MMD patient with the same clinical condition was reported: this patient developed cognitive decline accompanied by brain atrophy due to cerebral hyperperfusion syndrome after direct revascularization surgery [27]. Further, a study using animal models demonstrated that cerebral hyperperfusion following reperfusion after 3 days of hemispheric hypoperfusion induces white matter injury, inflammation, and subsequent cognitive decline as well as blood-brain barrier breakdown [28]. Therefore, postoperative cerebral hyperperfusion may produce wide-

![Fig. 5. A 35-year-old woman with ischemic MMD who underwent direct revascularization surgery in the left cerebral hemisphere and exhibited improved cognition at the end of the 5-year follow-up period. Formation of collateral flow from direct revascularization is identified when MR angiograms are compared before surgery (left end, upper) and at the end of the 5-year follow-up (left end, lower). Blood flow in the left frontal lobe is decreased relative to that in the left cerebellar hemisphere on brain perfusion SPECT before surgery (second from the left). The blood flow is increased on the day after surgery (second from the right), and this increased blood flow is maintained at the end of the 5-year follow-up period (right, end).]
spread damage to the ipsilateral cerebral hemisphere, resulting in irreversible cognitive decline.

Another important result of our study was an increase in CBF in the affected cerebral hemisphere in patients who showed cognitive improvement at 5 years. Previous studies have demonstrated improved cerebral oxygen metabolism along with increased CBF after direct revascularization surgery in the cerebral hemisphere with misery perfusion caused by MMD [29]. This improved metabolism is accompanied by improved postsurgical cognitive function [11]. Our observations are consistent with these previous reports and suggest that improvements in metabolism may be retained for a long time. On the other hand, CBF in most patients with reduced cognitive function was under the preoperative value 5 years later. Two pathophysiologically distinct conditions may result from reduced CBF: misery perfusion as a result of hemodynamic compromise and matched hypometabolism [30]. A prospective cohort study was performed that enrolled adult patients with ischemic MMD who were treated with medication only. Results showed that upon development of subsequent ischemic events, the affected cerebral hemisphere shows new misery perfusion, and patients without misery perfusion do not experience ischemic events. Thus, new development of misery perfusion may predict additional ischemic events in adult patients with ischemic MMD [3, 4]. None of the patients in our current study who exhibited reduced CBF at the end of the 5-year follow-up exhibited additional ischemic events and thus may not show misery perfusion. In contrast, for matched hypometabolism, damage to neurons leads to decreased metabolism in the cerebral cortex even if the cortex appears normal [31]. In this situation, CBF and cerebral metabolism are decreased in parallel [31]. Therefore, de-

**Fig. 6.** A 44-year-old woman with ischemic MMD who underwent direct revascularization surgery in the right cerebral hemisphere and exhibited cognitive decline at the end of the 5-year follow-up period. Formation of collateral flow from direct revascularization is identified when MR angiograms are compared before surgery (left end, upper) and at the end of the 5-year follow-up (left end, lower). Blood flow in the right frontal lobe is decreased relative to that in the left cerebellar hemisphere on brain perfusion SPECT before surgery (second from the left). Hyperperfusion develops in the right frontal lobe on the day after surgery (second from the right), and blood flow in the right cerebral hemisphere is decreased more prominently at the end of the 5-year follow-up (right, end) than before surgery.
creased CBF at the end of the 5-year follow-up may indicate decreased cerebral metabolism, which leads to decreased cognitive function. In such patients, CBF 2 months after surgery was higher than the presurgical value [10], and CBF may gradually decrease over 5 years along with a decrease in cerebral metabolism.

**Conclusion**

One-third of adult patients with cerebral misery perfusion due to ischemic MMD who underwent direct revascularization surgery exhibited cognitive improvement, and one-third patients exhibited decline at the end of the 5-year follow-up. The results also indicated that the former and latter patients had increased and decreased CBF, respectively, in the affected cerebral hemisphere at the end of the 5-year follow-up compared with preoperative brain perfusion.

**Statement of Ethics**

This prospective observational study was carried out in accordance with the guidelines of the World Medical Association and Declaration of Helsinki, and the protocol was reviewed and approved by the Iwate Medical University School of Medicine institutional Ethics Committee (No. H17-26). Written, informed consent was obtained from all patients or their next of kin before the study began.

**Conflict of Interest Statement**

The author (Kuniaki Ogasawara) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: consigned research funds from Nihon Medi-Physics Co., Ltd. The corresponding author (Kuniaki Ogasawara) is one of the present journal’s editorial board members.

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**Author Contributions**

Shun Uchida and Kuniaki Ogasawara contributed to conception and design, acquisition of data, analysis and interpretation of data, drafting the article critically for important intellectual content, and the final approval of the version to be published. Yoshitaka Kubo, Masahiro Yabuki, Shunrou Fujiiwara, Kenji Yoshida, and Masakazu Kobayashi contributed to conception and design, revising the article critically for important intellectual content, and the final approval of the version to be published. Daisuke Oomori, Kei Kitakami, and Kazunori Terasaki contributed to acquisition of data, revising the article critically for important intellectual content, and the final approval of the version to be published. All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Data Availability Statement**

All data generated or analyzed during this study are not publicly available on ethical grounds. However, inquiries regarding these data can be directed to the corresponding author.

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