INTRODUCTION

Moyamoya disease (MMD) is a rare bilateral cerebrovascular occlusive disorder of unknown etiology; it causes hemodynamic dysfunction that leads to neurocognitive impairment. In addition, the neurocognitive impairment of adults with MMD is infrequently reported and, to date, has not been well described. We attempted to determine both the neurocognitive profile of adult moyamoya disease and whether a superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis can improve the neurocognitive impairment in exhibiting hemodynamic disturbance without stroke.

Preliminary Study of Neurocognitive Dysfunction in Adult Moyamoya Disease and Improvement after Superficial Temporal Artery-Middle Cerebral Artery Bypass

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Objective: Moyamoya disease (MMD) is a chronic cerebrovascular occlusive disease of unknown etiology. In addition, the neurocognitive impairment of adults with MMD is infrequently reported and, to date, has not been well described. We attempted to determine both the neurocognitive profile of adult moyamoya disease and whether a superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis can improve the neurocognitive impairment in exhibiting hemodynamic disturbance without stroke.

Methods: From September 2010 through November 2012, 12 patients with angiographically diagnosed MMD underwent STA-MCA anastomosis for hemodynamic impairment. Patients with hyperperfusion and impaired cerebrovascular reserve (CVR) capacity but without evidence of ischemic stroke underwent a cognitive function test, the Seoul Neuropsychological Screening Battery (SNSB). Five patients agreed to undergo a follow-up SNSB test. Data from preoperative and postoperative neurocognitive function tests were compared and analyzed.

Results: Five of 12 patients were enrolled. The median age was 45 years (range, 24–55 years). A comparison of preoperative to postoperative status of SNSB, memory domain, especially delayed recall showed significant improvement. Although most of the domains showed improvement after surgery, the results were not statistically significant.

Conclusion: In our preliminary study, large proportions of adult patients with MMD demonstrate disruption of cognitive function. This suggests the possibility of chronic hyperperfusion as a primary cause of the neurocognitive impairment. When preoperative and postoperative status of cognitive function was compared, memory domain showed remarkable improvement. Although further study is needed, neurocognitive impairment may be an indication for earlier intervention with reperfusion procedures that can improve cognitive function.

Key Words: Neurocognitive impairment · Moyamoya disease · STA-MCA anastomosis.
without stroke.

**MATERIALS AND METHODS**

**Patients**

From September 2010 through November 2012, we identified 12 adult patients with angiographic confirmation of MMD; we designed a prospective study to compare and analyze cognitive function in patients with hemodynamic impairment before and after STA-MCA anastomosis surgery. Five patients fulfilled the study criteria described below; all five were females with a median age of 43.2 (range, 24–51 years). Initial clinical symptoms leading to the neurocognitive evaluation included two or more of following symptoms: dizziness, headache, syncope, memory disturbance, and/or dysarthria. The mean educational level of these patients was 10 years. A summary of patient characteristics is presented in Table 1.

**Imaging studies**

All bypass surgeries were performed by one neurosurgeon. For preoperative evaluation, the patients underwent computed tomography 3D angiography (CTA), trans-femoral cerebral angiography (TFCA), brain perfusion single-photon emission computed tomography (SPECT) with and without acetazolamide injection, and magnetic resonance image (MRI) of the brain, which included following sequences: T1, T2, gradient echo (GRE), perfusion, and diffusion. Brain perfusion SPECT is a functional nuclear imaging technique performed to evaluate regional cerebral perfusion. We used SPECT Symbia dual e cam (Siemens Medical Solutions USA, Inc., Hoffmann Estates, IL, USA). The resting image is taken after injection of 15–30 mCi of 99mTc-hexamethylpropyleneamine oxime (HMPAO). The dynamic SPECT image is taken 10–20 minutes after intravenous injection of 1 g acetazolamide, which increases local pCO2 and causes arteriolar dilation; thus, allowing for assessment of cerebrovascular reserve. MRI perfusion and brain perfusion SPECT with and without acetazolamide were used to evaluate hemodynamic status. MR diffusion revealed the previous ischemic injury without acetazolamide, which increases local pCO2 and causes arteriolar dilation and causes arteriolar dysfunction if the z-score was 1 to 2 SDs below the normative mean; moderate dysfunction if the score was 2 to 3 SDs below the normative mean; and severe if the score was ≥3 SDs below the normative mean. Each domain provided raw data, which was converted to z-scores, based on published normative means.

| Table 1. Characteristics of patients (n=5) |
|------------------------------------------|
| **Year (years)** | **Sex** | **Education (years)** | **Initial clinical symptoms** | **Handedness** | **Occupation** | **Location of surgery** |
|------------------|---------|-----------------------|-----------------------------|----------------|----------------|------------------------|
| Case 1.          | 51      | F                     | 9                           | Memory disturbance | Rt.           | Waitress               | Lt.                     |
| Case 2.          | 46      | F                     | 2                           | Dizziness, headache | Rt.           | Retailor               | Rt.                     |
| Case 3.          | 24      | F                     | 15                          | Syncope, dizziness | Rt.           | Student (college)      | Rt.                     |
| Case 4.          | 46      | F                     | 12                          | Headache          | Rt.           | None                   | Lt.                     |
| Case 5.          | 49      | F                     | 12                          | Dyssarhria         | Rt.           | Sherman                | Lt.                     |
Statistical analysis

Data from preoperative and postoperative cognitive function tests were compared and analyzed. Statistical evaluation was performed using the Wilcoxon signed rank test. The level of significance was set at $p<0.05$. Statistical analyses were performed using the SPSS Statistics 20 (IBM Corp., Armonk, NY, USA).

RESULTS

Data from five patients were analyzed in the present study. In
all five cases, TFCA was performed prior to surgery to confirm the presence of an occlusive lesion (Fig. 1A). The unilateral STA-MCA bypass surgery was performed successfully without complications (Fig. 1B, C). A preoperative MRI diffusion study found no evidence of infarction (Fig. 1D). Preoperative perfusion MRI showed MTT and TTP prolongation (Fig. 1E, F). Brain perfusion SPECT with and without acetazolamide confirmed decreased reserve capacity in the right frontal lesion (Fig. 1G, H).

The postoperative TFCA showed adequate patency of the bypass; hemodynamic evaluation of the surgical sites via MRI perfusion and brain perfusion SPECT imaging with and without acetazolamide on postoperative day 7 showed improvement (Fig. 1I–L). The patients underwent a follow-up SNSB test within three months of the STA-MCA bypass surgery. Data from pre- and post-operative cognitive function tests were compared and analyzed (Fig. 2, 3).

Pre- and post-operative MR perfusion and brain perfusion SPECT showed postoperative improvement of hemodynamic status. The perfusion MRI and SPECT images were compared (Fig. 1E–L). The postoperative MRI perfusion showed improvement in the MCA region where the STA is connected to the 4th segment of the MCA branch. In addition, the SPECT image showed improvement in reserve capacity. The results of the MRI perfusion and SPECT images correlated well and documented the successful surgery result with improved progression of hemodynamic status. Comparison of pre- and postoperative cognitive function revealed SNSB improvement. Fig. 2 shows the comparison of preoperative and postoperative z-score mean standardized results of neuropsychological measurements and the differences of the two results in eight domains. In general all patient results improved postoperatively except general mental status. However, these findings only attained statistical significance in the memory domain. Visuospatial function, inhibitory control, and memory are frequently impaired domains. Few patients had severe dysfunction (≥3 SDs below the normative mean) in specific domain. However, impairment of visuospatial function and inhibitory control domain were patient-specific rather than general; thus, the p-values of these domains were not statistically significant. For example, one patient scored -11.46 on the preoperative evaluation; it improved to -2.08 postoperatively, which represented an approximately 9 SD improvement in the visuospatial domain. The memory domain was the most improved domain following STA-MCA bypass, specifically in delayed recall. The visual memory domain improved in four of five patients. The memory domain was specifically analyzed in Fig. 3. Although both immediate and delayed recall improved, the improvement of delayed recall was statistically significant (p-values=0.038 for verbal memory and 0.042 for visual memory) together with the improvement of subjective symptoms.

**DISCUSSION**

MMD is a rare cerebrovascular disorder characterized by progressive stenosis and occlusion of the internal carotid and the anterior and middle cerebral arteries. MMD is diagnosed via confirming the cerebrovascular occlusion of the distal internal carotid artery (ICA), proximal anterior cerebral artery (ACA) and/or the MCA via CTA, or TCFA. MRI perfusion or brain perfusion SPECT with and without acetazolamide is used to evaluate the hemodynamic status of the brain due to chronic hypoperfusion from diminished vascularity. Usually, MMD is diagnosed after a cerebral stroke in adults and a transient ischemic attack in children. The need for revascularization surgery has been
The results of the postoperative cognitive function test showed substantial improvement in the memory domain to a level of 99.24, which is based on the analysis of 447 healthy subjects. The standard index of cognitive function evaluation for assessing cognitive function in Korea for assessing cognitive function in stroke-free adults.

In children with MMD, diminished cerebral perfusion in MMD may lead to regional dysfunction in the absence of overt infarction. Among pediatric patients, intellectual ability is an ongoing focus of research. Thus, there are many reports assessing intellectual ability. Furthermore, cognitive impairments are not infrequent in children with MMD, despite normal general intellectual function. William et al. reported that children with MMD demonstrated lower intelligence and poorer executive function than test standardization samples. It is a recent concept that in adult MMD patients, chronic hypoperfusion can lead to cognitive impairment. Jefferson et al. emphasized the importance of cognitive function evaluation for chronic cerebrovascular disorders including MMD. Karzmark et al. documented that MMD in adults can impair cognition, particularly in the domain of executive function. Calviere et al. reported a high rate of cognitive impairment in six of 10 patients that significantly affected executive function.

Frequently, the cognitive impairment in adult patients is underestimated and neglected. Mogensen et al. reported decreased executive function in an adult population with MMD; it was the most strongly associated with secondary damage to the brain parenchyma, manifested by white matter disease or cortical stroke. Diagnosis of MMD in adult patients following stroke, either ischemic or hemorrhagic, obscures the influence of chronic hypoperfusion; consequently, cognitive dysfunctions are frequently not assessed or misinterpreted. Because the cognitive impairment slowly progresses over time and many patients assume that the symptoms are due to the aging process, the cognitive impairment in adult MMD patients is often not recognized.

There are some reports, both in children and adults, that note that cerebral revascularization may slow or arrest progression and perhaps even improve cognitive function; however, these studies do not clearly define the effects of stroke. Lee et al. analyzed improvement in the level of intelligence after indirect bypass surgery in pediatric MMD patients: they found that the long-term outcome of cognitive function was poorer in the nonsurgical group. These reports were limited to pediatric patients. In the current study, the samples were adult MMD patients without a history of a cerebrovascular event, and all patients enrolled in this study were evaluated for an undiagnosed stroke event and presented with normal hearing and visual status. We analyzed the cognitive improvement comparing pre- and post-revascularization surgery in stroke-free adults.

The SNSB is one of the most commonly used neuropsychological tests in Korea for assessing cognitive function; the normal range is based on the analysis of 447 healthy subjects. The standard test indices are age, education, and sex (adjusted to interpretation). Comparing the pre- and post-operative cognitive function test, the results of postoperative cognitive function test showed no significant improvement in the memory domain together with the recovery of the patients’ subjective symptoms. The results of the postoperative cognitive function test showed improvement, compared to preoperative status. The neurocognitive impairment differs between adult and pediatric populations. Intelligence is the most affected cognitive parameter in children, whereas executive function is the most impaired parameter in adults. The pediatric samples with MMD had an almost normal, age-appropriate level of intelligence and neurocognitive function before surgery and their cognitive function appeared to be maintained postoperatively. For adult MMD patients, the focus of the cognitive impairment should be on executive function and memory domains. The preoperative results of impaired cognition domains were similar to those of previous studies. Mental efficiency, executive function, and expressive language abilities were found to be the domains most affected in previous reports. Memory and basic sensory capacities were reported to be relatively intact in other studies, which differed from the present study. Weinberg et al. concluded that all cognitive parameters tested, memory showed the lowest rate of impairment; therefore, the medial temporal function is relatively spared in patients with MMD. In contrast, our study showed that memory and visuospatial functions were the most impaired, followed by executive function. In all five patients, statistically significant improvement was found in the memory domain, specifically delayed recall memory. Since MMD is a disease primarily affecting the distal ICA and proximal middle and anterior cerebral artery, usually the ACA and MCA regions and their watershed areas are affected. The impairment of frontal perfusion in MMD can be explained by the distribution of arterial occlusive lesions, usually limited to the ICAs, and sparing the posterior circulation, and the development of a pial collateral supply from the posterior cerebral arteries to the middle and anterior cerebral arteries. As a result, the executive, memory domains could be impacted by chronic hypoperfusion; thus, they would benefit the most from revascularization.

Our study has several limitations. First, there was a limitation in patient selection. Because all the patients were selected from symptomatic individuals who sought medical care, there was selection bias. Enrolled samples were biased toward patients with the greatest neurocognitive impairment, with variable clinical symptoms such as headache, dizziness, or even transient ischemic attacks. Second, because MMD is a rare disease it does not comprise an adequate sample size to detect potential differences in race, gender, or institution. Third, our study is limited to patients who underwent revascularization surgery. Fourth, the difference of neurocognitive impairment between the non-surgical group and the surgical group were not compared. Therefore, we do not have complete understanding of the progression of cognitive impairment under conservative management. Fifth, SNSB can evaluate all cognitive domains; however, the battery does not provide a global cognitive function (GCF) score. The standard index of age range was 55 to 80 years with a mean age of 67.63 years (female: 67.51; male 67.79). The mean age of our patients was 43.2 years, which was younger than the standard index of the examined cohort; there is uncertainty in regard to the results regarding the age factor. The results may appear milder than the actual
degree of cognitive impairment. Also the duration to complete the exam is approximately 90–120 minutes. For some patients, it is a long enough time for inattention to occur, which would compromise the results. Further studies that comprise a larger patient population with pre- and post-operation neurocognitive evaluation are essential for the conduction of a multivariable analysis.

CONCLUSION

In our preliminary study, we found that a large proportion of patients with adult MMD demonstrated disruption of neurocognition. Cognitive impairment could ensue after a focal neurologic deficit: this could be followed by a hemorrhagic event or infarction. However, we also suggest the possibility of chronic hypoperfusion as the primary cause of the cognitive impairment in MMD. The result of the SNSB comparing preoperative neurocognitive deficits and postoperative neurocognitive improvements in the memory domain. Although further study is needed, the importance of performing a neurocognitive evaluation should be emphasized. This would more comprehensively assess the full clinical impact of MMD; furthermore, cognitive dysfunction may be an indicator for earlier intervention with perfusion procedures that would benefit cognitive function.

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