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ORIGINAL ARTICLE

# Long-term follow-up of pediatric moyamoya disease treated by combined direct–indirect revascularization surgery: single institute experience with surgical and perioperative management

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**Abstract** Moyamoya disease (MMD) is a rare occlusive cerebrovascular disease that mainly presents in children as cerebral ischemia. Prompt treatment with either a direct or indirect revascularization procedure is necessary for children with MMD in order to prevent repeated ischemic events. We herein present our experience with combined direct and indirect bypass surgery for the treatment of pediatric MMD as well as our uniquely designed perioperative protocol. Twenty-three patients with MMD, aged between 2 and 16 years old (mean 9.36), underwent 38 combined bypass procedures between 2008 and 2015. All patients underwent single superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis combined with encephalo-duro-myo-synangiosis (EDMS). The perioperative management protocol was stratified into two unique eras: the first era with normotensive care and the second era with strict blood pressure control (systolic 100–130 mmHg) and routine aspirin administration. Patients were followed after surgery for a period ranging between 3 and 131 months (mean 77 months) in yearly clinical and radiological follow-ups. Three postoperative complications were observed: two cases of cerebral hyperperfusion (2/38, 5.3 %) and one case of perioperative minor stroke (1/38, 2.6 %), two of which were in the first era. No strokes, either ischemic or hemorrhagic, were observed in the follow-up period, and the activity of daily living as shown by the modified Rankin Scale improved in 20 patients, with no deterioration being observed in any of our patients. STA-MCA bypass with EDMS is safe and effective for the management of pediatric MMD and provides long-term favorable outcomes. Perioperative care with blood pressure control combined with the administration of aspirin may reduce the potential risk of surgical complications.

**Keywords** Moyamoya disease · Pediatric moyamoya · Bypass

**Abbreviations**

| | |
|---|---|
| ECA | External carotid artery |
| EDAS | Encephalo-duro-arterio-synangiosis |
| EDMS | Encephalo-duro-myo-synangiosis |
| ICA | Internal carotid artery |
| MCA | Middle cerebral artery |
| SPECT | Single photon emission computed tomography |
| STA | Superficial temporal artery |

## Introduction

Moyamoya disease (MMD) is a rare cerebrovascular occlusive disease that affects children and adults and is characterized by steno-occlusive changes in the terminal portion of the internal carotid artery (ICA) and an abnormal vascular network at the base of the brain [1]. MMD has a unique and dynamic pathophysiology, in which blood supply in the brain is shifted from the internal carotid (IC) system to the external carotid (EC) system [2].

The philosophy for the treatment of MMD entails supporting the failing arterial supply to the brain in the transition period during which the blood supply is shifted from the IC system to the EC system. Thus, by performing bypass surgery, the natural pathophysiological course of the disease is supported during its vulnerable stages [3, 4].

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In young patients, MMD exhibits rapid progression, with more frequent preoperative infarctions resulting in a poorer clinical outcome [5], and the younger the patient, the more aggressive the clinical course is [6]. This aggressiveness among younger patients justifies prompt surgical treatment; however, it has not yet been established whether technically easier indirect bypass surgery is sufficient to alleviate symptoms with the risk of delayed revascularization and the lack of an impact on hemorrhagic MMD or if direct bypass surgery needs to be performed in order to attain rapid cerebral blood flow (CBF) reconstitution with the obvious risk of hyperperfusion syndrome in addition to its technical difficulty, particularly in younger children [1, 4, 6, 7].

We herein report our experience of the treatment of pediatric MMD with a combined direct–indirect bypass procedure and the results obtained from a long-term follow-up extending over one decade in order to show the benefits and outcomes of this technique in the treatment of children with MMD.

## Patients and methods

This study included a retrospective analysis of data on 23 patients managed for MMD by bypass surgery for 38 hemispheres between 2004 and 2015. All patients had surgeries performed by the same surgeon (M.F.). Patient ages ranged between 2 and 16 years at surgery with a mean of 9.36 years. Patients were divided into 2 groups according to age at presentation: group 1: childhood presentation before the age of 12 (15 patients) and group 2: adolescent presentation between the ages of 12 and 16 (8 patients).

**Presentation** All patients presented with ischemic symptoms, with 6 patients having complete strokes and 17 transient ischemic attacks (TIA). Of the six patients who presented with infarctions, one had infarctions in both hemispheres, while the remaining five had a unilateral presentation. The preoperative modified Rankin scale (mRS) was 3 in 2 cases, 2 in 5 cases, and 1 in 16 cases. mRS 1 indicates patients with TIA only, while patients with complete stroke were classified as mRS 2 or 3 depending on the size of the stroke, its severity, and its occurrence in eloquent or non-eloquent areas. Five patients presented with complete stroke in childhood before 12 years of age, while one patient presented at adolescence.

Seven out of 23 patients had unilateral MMD, while the remainder had bilateral disease presentation. None of the patients had hemorrhagic presentation. All patients satisfied the diagnostic criteria of the Research Committee on Spontaneous Occlusion of the Circle of Willis of the Ministry of Health, Labor, and Welfare, Japan, except for one patient with akin-MMD with neurofibromatosis type-I.

**Diagnostic imaging** All patients were subjected to 1.5- or 3.0-tesla magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) prior to being diagnosed, and the diagnosis reached was reinforced by conventional catheter-based angiography in patients older than 13 years of age. Very young patients and those suspected of morbidity related to catheter angiography were only diagnosed with MMD based on MRI/MRA appearances. Preoperative CBF was measured in all patients using N-isopropyl[123I]-p-iodoamphetamine ($^{123}$I-IMP-SPECT). A quantitative analysis by an autoradiographic (ARG) method was performed in most patients.

**Surgery** All 23 patients underwent superficial temporal artery-middle cerebral artery (SAT-MCA) anastomosis combined with encephalo-duro-myo-synangiosis (EDMS) on the 38 affected hemispheres, while 1 hemisphere besides the present series was managed by EDMS based on intraoperative findings. If one side was more clinically symptomatic than the other, we started with the dominant hemisphere. Following craniotomy around the Sylvian fissure end, direct bypass was performed between one branch of STA and a branch of the M4 segment of the MCA. Indirect bypass was then performed by inverting the edges of the dural flaps inside and laying the temporalis muscle as a pedicle flap after splitting the muscle on the surface of the brain (EDMS) [8]. The inner bone layer of the bone flap was then thinned out by drilling to prevent compressing the muscle pedicle and subsequent muscle swelling and brain compression [8]. Detailed surgical techniques were described elsewhere [9].

In patients with bilateral symptoms, surgery was initially performed on the more symptomatic side. If the patient exhibited equal symptomatology bilaterally, we initiated surgery on the dominant hemisphere. A second surgery was performed 2 to 4 weeks after the first surgery. During this period, patients were maintained under antiplatelet therapy coverage (low-dose aspirin), which was stopped 3 days before the second surgery and restarted the day after surgery.

**Perioperative care** Perioperative care was divided into two eras, each of which had a different protocol (Table 1). The early era was between 2004 and 2008, during which no perioperative antiplatelet coverage was given and blood pressure was not routinely lowered, except in selected patients with hyperperfusion. The late era was between 2008 and the time of this study, during which blood pressure was routinely between 100 to 130 mmHg (systolic), and an antiplatelet agent was administered from postoperative day 1 (POD 1) in all cases [10]. In 2010, minocycline hydrochloride, a neuroprotective antibiotic agent, was introduced along with blood pressure control and antiplatelet agents [11].

**Table 1** Summary of the results of 38 direct/indirect revascularizations managed by two distinct perioperative management protocol

| | 1st Era | 2nd Era |
|---|---|---|
| Patients: | | |
| No of patients | 9 | 14 |
| Male | 4 | 3 |
| Female | 5 | 11 |
| No. of hemispheres | 17 | 21 |
| Age at presentation | | |
| Range | 2–8 years | 8–16 years |
| Mean | 6.22 years | 12 years |
| Presentation | | |
| TIA | 5 | 12 |
| Stroke | 4 | 2 |
| Unilateral | 1 | 6 |
| Bilateral | 8 | 8 |
| Perioperative complications | | |
| Stroke (minor) | 1 | 0 |
| HPS | 1 | 1 |
| Preoperative mRS score | | |
| 1 | 5 | 11 |
| 2 | 3 | 2 |
| 3 | 1 | 1 |
| Postop mRS score | | |
| 0 | 5 | 13 |
| 1 | 2 | 0 |
| 2 | 2 | 1 |
| Postoperative outcome | | |
| Excellent | 6 | 13 |
| Good | 3 | 1 |
| Poor | 0 | 0 |

TIA transient ischemic attack, HPS hyperperfusion syndrome, mRS modified Rankin Scale

**Postoperative radiological follow-up** Following surgery, all patients underwent immediate computed tomography (CT) to rule out hemorrhaging and establish a baseline CT to be referred to in case of any perioperative or delayed postoperative complications. CBF measurements were performed on days 1 and 7 postsurgery by $^{123}$I-IMP-SPECT in all cases. In all cases, 1.5- or 3.0-tesla MRI and MRA were routinely performed 2 days after surgery. If the bypass signal was equivocal 2 days after surgery, we repeated MRA in the subacute stage. MRI included diffusion-weighted images (DWI), fluid attenuated inversion recovery (FLAIR), T1-/T2-weighted images, and T2*-weighted images.

## Follow-up

Patients were followed-up for periods ranging between 3 months, for the most recent case, and 131 months (mean 77 months). Patients were followed clinically for the length of the follow-up by yearly visits to the hospital, and those who were unable to come to our hospital had their clinical examination conducted by a local neurosurgeon who, in turn, conveyed its results. Patients were examined for any signs of cognitive delay or permanent neurological defects and were questioned regarding the development of any new symptoms and their scholastic and academic performances.

Patient outcomes were classified as 1—excellent: the disappearance of preoperative symptoms, 2—good: the presence of some neurological deficits that are not limiting. Limiting neurological deficits were defined as those causing mental or motor limitations to the full independence of daily living and function of the patient, such as hemiparesis or mental retardation. 3—Fair: the presence of neurological deficits that are limiting with the disappearance of preoperative symptoms, and 4—Poor: persistence of preoperative neurological symptoms. Radiological follow-ups were conducted in a yearly MRI/MRA examination in order to reveal silent strokes that may have been subclinical and, henceforth, missed.

## Results

### Surgical procedure

Twenty-three patients underwent 39 surgeries for MMD, with a unified surgical protocol of combined direct and indirect bypass. All bypass procedures were successful, except for one in which intraoperative repeated bypass graft thrombosis raised concerns regarding the postoperative course of the bypass. Based on that observation, the direct bypass was disconnected, the donor vessel was reconstructed, and only an indirect bypass was performed. The patient did not develop any complications postoperatively from the direct bypass trial.

### Perioperative complications

Three patients developed transient neurological deterioration following surgery (Table 1). This was related to hyperperfusion syndrome (HPS) in two patients (2/39, 5.3 %) and perioperative infarction in one patient (1/38, 2.6 %). Two of the patients were from the first era of perioperative management. None of our patients developed postoperative hemorrhagic complications. According to the age group, all complications occurred in the childhood group, with none being observed in the adolescent group (Table 2).

Other minor complications included cerebrospinal fluid subcutaneous effusion in one patient, which spontaneously resolved, and wound granuloma in another, which was removed by minor surgical debridement. Another patient developed asymptomatic occipital arteriovenous malformation 4 years after surgery, which was detected in a routine follow-up [12].

**Table 2** Summary of the results of 38 direct/indirect revascularizations distributed according to age group

| | Childhood | Adolescent |
|---|---|---|
| Patients | | |
| No. of patients | 15 | 8 |
| Male | | |
| Female | | |
| No. of hemispheres | 27 | 12 |
| Age at presentation | | |
| Range | 2–11 | 12–16 years |
| Mean | 7.47 years | 14 years |
| Presentation: | | |
| TIA | 10 | 11 |
| Stroke | 5 | 1 |
| Unilateral | 3 | 4 |
| Bilateral | 12 | 4 |
| Perioperative complications | | |
| Stroke (minor) | 1 | 0 |
| HPS | 2 | 0 |
| Preoperative mRS score | | |
| 1 | 10 | 6 |
| 2 | 4 | 1 |
| 3 | 1 | 1 |
| Postop mRS score | | |
| 0 | 11 | 7 |
| 1 | 2 | 0 |
| 2 | 2 | 1 |
| Postoperative Outcome | | |
| Excellent | 12 | 7 |
| Good | 3 | 1 |
| Poor | 0 | 0 |

TIA transient ischemic attack, HPS hyperperfusion syndrome, mRS modified Rankin Scale

Regarding the outcomes of bypass in patients who completed direct/indirect revascularization procedures, the patency rate as defined by the confirmation of STA-MCA bypass signals in the acute or subacute stage by MRA was 100 %. In the chronic stage, some patients developed severe pial synangiosis and STA-MCA bypass became invisible in rare cases.

## Long-term outcomes

mRS improved in 20 patients and remained stable in 3. No mRS deterioration was observed in any of our patients. mRS improved from 1 to 0 in 15 patients, from 2 to 0 in 1 patient, from 2 to 1 in 2 patients, and from 3 to 2 in 2 patients (Table 1).

Outcomes were excellent in 19 patients and good in the remaining 4, with no poor outcomes being recorded in any of our patients. Although no specific cognitive testing was performed, all patients reported acceptable normal scholastic performances while attending a regular education system, with some patients now in high school and some starting university. None of our patients reported a need for special education at any point of their follow-up. All patients were followed to date, except for one patient who was lost to the follow-up due to the Great Eastern Japan earthquake in 2011. However, his name was not on the dead persons list released by the Japanese government.

### *Representative cases*

Case 1: A 7-year-old boy initially had crescendo TIA with repeated transient weakness in his hands, predominantly on the left side. Initial MRA revealed stenosis of the bilateral internal carotid arteries at their terminal portion and abnormal vascular networks at the base of the brain (Fig. 1a), which led to the diagnosis of MMD. MRI revealed ischemic changes in the bilateral paraventricle area (Fig. 1b). Preoperative $^{123}$I-IMP-SPECT indicated the presence of hemodynamic compromise in the bilateral hemispheres. He underwent right STA-MCA anastomosis with EDMS, and left STA-MCA anastomosis with EDMS was attempted 1 month later, both of which resulted in uneventful postoperative courses. The patient graduated junior high school and now goes to a regular high school. The patient has not experienced stroke in the follow-up period of 10 years. The most recent MRA, performed 10 years after bilateral surgeries, demonstrated that bilateral direct/indirect revascularization is well-developed, as shown by the signals of the STA, middle meningeal arteries, and deep temporal arteries (yellow circles in Fig. 1c). MRI showed no evidence of newly formed ischemic changes after surgeries (Fig. 1d).

Case 2: A 13-year-old girl initially had transient aphasia and motor weakness in her right hand. MRA revealed stenosis of the bilateral internal carotid arteries at their terminal portion and abnormal vascular networks at the base of the brain. Catheter angiography confirmed the definitive diagnosis of MMD (data not shown). In light of the hemodynamic compromise on the left hemisphere by $^{123}$I-IMP-SPECT, she underwent left STA-MCA anastomosis with EDMS without complications. The asymptomatic right side was not operated on and we continued yearly follow-ups by MRI/MRA. MRA 5 years after surgery showed the STA-MCA bypass as thick high signal intensity (Fig. 2a, arrow), and FLAIR did not detect any ischemic change or ivy sign (Fig. 2b). $^{123}$I-IMP-SPECT performed 5 years after left surgery demonstrated the normalization of CBF in the hemisphere operated on (Fig. 2c). She graduated from a regular high school and entered university 5 years after surgery.

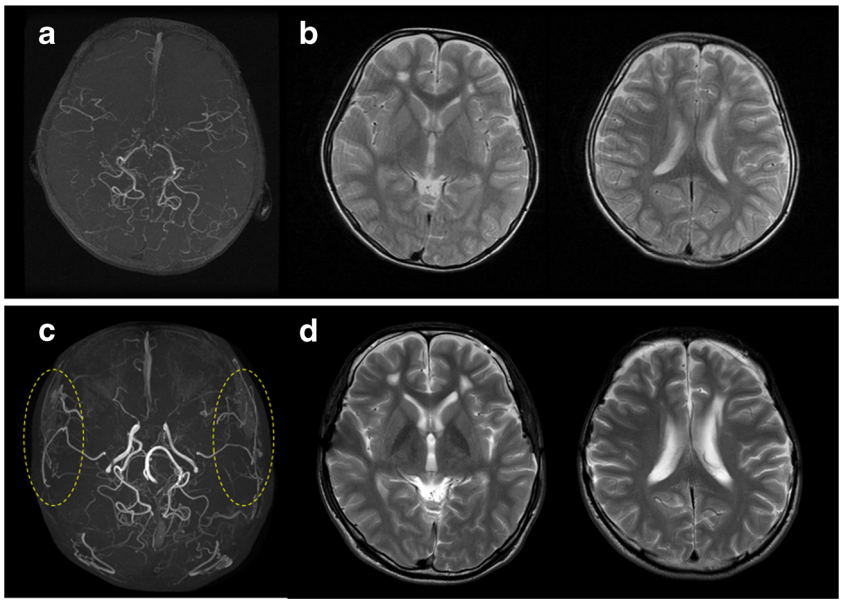


**Fig. 1** Case 1: **a** Preoperative MRA demonstrating stenosis of the bilateral terminal internal carotid arteries. **b** T2-weighted imaging (MRI) showing ischemic changes in the bilateral paraventricle area. **c** MRA 10 years after bilateral STA-MCA anastomosis with EDMS, demonstrating that bilateral direct/indirect revascularization is well-developed (*yellow circles*). **d** T2-weighted imaging (MRI) showing no evidence of newly formed ischemic changes after surgeries

## Discussion

In the present study, we presented our successful results on the management of MMD, in which there were only 3 perioperative complications among 38 direct/indirect combined surgeries. While considering the protocol era, ischemic complication was only observed in the early period of this study, while none were observed with the instillation of the strict perioperative care protocol described above. These results may be interpreted as 100 % satisfactory outcomes given the parameters considered in different studies [6, 7]. All patients reported good, satisfactory school performances. None of the patients needed special forms of education or experienced worsened school performances. The surgical treatment of MMD essentially involves bypass, whether direct, indirect, or a combination of the two. While the superiority of direct/combined over indirect bypass has been reported in adults [13], a debate remains regarding the best strategy for the pediatric population. The reason for this debate is related to the technical difficulties associated with performing direct bypass on small and fragile moyamoya vessels, particularly in younger children [7, 14], with good outcomes being achieved with indirect bypass surgery in between 58 and 86 % of patients depending on the age group and presentation [6, 7, 15]. The long-term effects of strokes in children and the ability to lead a normal independent life are the main concerns following surgery in young children, and hence, the value of long-term follow-up studies is appreciated more when considering optimal MMD treatments. Bao et al. [7] previously reported that 86 % of the 288 pediatric patients with MMD who underwent indirect bypass (EDAS) went on to have independent lives with no significant disabilities. Phi et al. [16] followed 123 pediatric MMD patients who underwent indirect bypass into adulthood and reported that 5.6 % had poor outcomes and 18.7 % fair outcomes. Phi et al. also conducted a questionnaire regarding scholastic performances among their patients; among the 61 patients who answered the questionnaire, 28 % reported worsened school performances, while 48 % reported no change and 15 % reported improved performances [16]. Kuroda et al. [17] analyzed factors with the potential to adversely affect intellectual performance following surgery in young patients and reported that preoperative complete stroke and small craniotomy surgery with indirect bypass were factors related to poorer intellectual outcomes. Previous studies showed that indirect procedures are associated with poorer cognitive outcomes than direct surgery is. One reason for this may be the limitation of revascularization to the area under craniotomy in indirect surgery, as opposed to direct bypass, which markedly improves blood flow to the hypoperfused brain, and this is also observed even if frontal lobe revascularization is performed in combination with usual EDAS or EMS. [18] In the present study, outcomes were excellent in 19 patients (19/23, 82.6 %) and good in 4 (4/23, 17.4 %). Although some patients developed sufficient pial synangiosis in the long-term follow-up such that direct bypass was no longer visible, we attributed the good results obtained in our study to early perfusion restoration caused by direct bypass, followed by the chronic development of pial synangiosis. This immediate perfusion restoration protected patients from postoperative ischemic strokes that occur during the "waiting period" for the development of pial collaterals.

Complications following surgery may grossly affect the growing brain of a child, and while direct bypass is considered more difficult to accomplish, it has lower rates of perioperative stroke than indirect bypass has [19]. This has been attributed to the immediate restoration of blood flow following the establishment of direct bypass. Direct bypass itself is not free from complications; ischemic complications may occur,

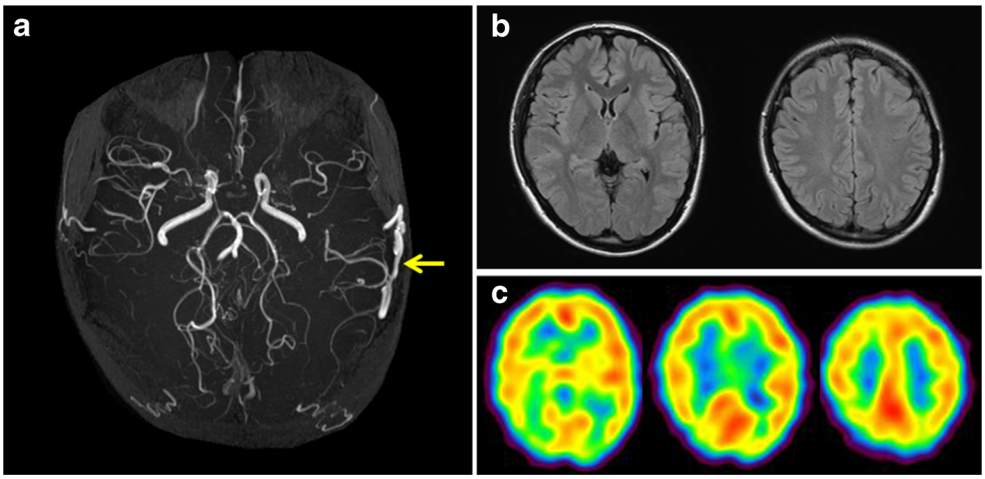


**Fig. 2** Case 2: Postoperative examination 5 years after left STA-MCA anastomosis, performed at the age of 13. **a** MRA demonstrating the bypass as a thick high signal intensity (*arrow*). **b** FLAIR imaging indicating no ischemic change or ivy sign. **c** $^{123}$I-IMP-SPECT performed 5 years after left surgery demonstrating the normalization of CBF in the hemisphere operated on

leading to strokes, due to thromboembolism from the anastomosis or "Watershed shift phenomenon" [2, 5]. Furthermore, cerebral hyperperfusion may follow direct bypass in children, although at lower rates than that in adults [1, 2]. A carefully designed postoperative protocol and close monitoring are important for avoiding these complications. In the present study, we observed 2 cases of postoperative hyperperfusion syndrome in 38 surgeries (5.3 %), and 1 case of delayed ischemic stroke in the form of cortical pseudolaminar necrosis (2.6 %) [1]. These three patients developed transient neurological deterioration following these events; however, no long-term sequelae followed. The surgical protocol remained essentially the same throughout the course of this study, with combined direct and indirect bypass being the first choice, and was successfully achieved in 38 out of 39 procedures (97.4 %). The single failure in performing direct bypass was caused by the repeated formation of intraoperative thrombi at the anastomosis site, which we were unable to overcome despite several attempts at flushing with heparinized saline and reanastomosis, which eventually resulted in the safe choice to convert to indirect bypass. This particular patient did not develop any sequelae from the failed bypass procedure and his postoperative course was uneventful.

In our literature review, we were unable to find special considerations for specific perioperative protocols, and while the surgical protocols are essentially the same, we consider our unique protocol to be the reason for less morbidity and superior intellectual outcomes in the long term in the present study. Our perioperative care protocol, unlike our surgical protocol, evolved over the course of this study in order to counteract the above-described complications associated with direct bypass. The postoperative protocol initially entailed maintaining normotensive conditions in subsequent surgery. This was later changed when prophylactic blood pressure lowering (<130 mmHg systolic BP) was adopted. We previously demonstrated the value of prophylactic blood pressure lowering in decreasing the incidence of symptomatic cerebral hyperperfusion more than maintaining normotensive conditions, as demonstrated in postoperative SPECT studies [10]. Minocycline hydrochloride, a synthetic tetracycline, was later introduced as part of the perioperative protocol to prevent focal neurological deficits from cerebral hyperperfusion; it was intravenously infused intraoperatively and postoperatively at a dose of 200 mg/day. Minocycline, by blocking the expression of matrix metalloproteinase (MMP)-9, has a neuroprotective role because it maintains the blood–brain barrier, thereby reducing the risk of vasogenic edema and hemorrhagic conversion; however, it is more beneficial in adult patients than in pediatric patients [11, 20]. Other therapies that are used in our protocol involve the free radical scavenger edaravone to counteract the deleterious effects of reperfusion injury on chronically ischemic brains [1] and antiplatelets to prevent thromboembolic events [2]. These also need to be combined with adequate fluid balancing and oxygenation. The value of such a strict perioperative protocol is apparent from the rates of complications between the two eras; we only observed three bypass-related complications (two hyperperfusion, one ischemic): two in the first era (2/17, 11.8 %) and one in the second era (1/21, 4.8 %). This result shows the benefits gained from employing various strategies to counteract the deleterious effects of the sudden perfusion of chronically hypoperfused MMD brains. A confounding issue that faces surgeons is what to do during the latency period between the first and second surgeries in patients with bilateral MMD. In our experience, coverage with low-dose aspirin and sufficient hydration may prevent ischemic symptoms during this period. In patients with severe bilateral CBF decreases, blood pressure was maintained between 110 and 130 mmHg and was not allowed to drop to lower than that level [10]. No ischemic complications were observed during the latency period between the first and second surgeries. Another issue that may face the treating team after surgery is postoperative anemia, which increases the predisposition of patients to ischemic events. While no patients in our series developed anemia

following surgery, our protocol for such cases (hemoglobin level less than 8 mg/dl) is to promptly perform blood transfusions.

The natural history of MMD is generally more aggressive in the pediatric population than in adults [6]; however, the incidence of postoperative complications appears to be higher in adults than in children. In a previous study, we presented our findings of direct revascularization in 106 consecutive patients (150 hemispheres) [3]. We observed 27 incidents of postoperative temporary neurological deterioration due to focal cerebral hyperperfusion syndrome in 26 patients. Twenty-five out of the 27 incidents occurred in adults even though the surgical and perioperative protocols were essentially the same. Guzman et al. [21], in their series of 329 patients treated mostly by direct bypass, reported 15 incidents of morbidity and/or mortality, with only 3 of which involving pediatric patients. In concordance with these findings, Kazumata et al. [19] reported higher rates for postoperative stroke in adult than in pediatric patients. There are currently no clear reasons for this difference because the pathophysiological mechanisms responsible for MMD are essentially considered to be the same in pediatric and adult patients. We speculate that these differences may be related to some subtle pathological differences between the two age groups that have not yet been identified or to the plasticity of a child's brain and its growing dynamics that set it apart from the adult brain. In the present study, complete stroke occurred more often in childhood than in adolescence (five versus one), and we also observed postoperative complications in the childhood group, but not in the adolescent group, which indicates that adolescent patients are similar to adults in terms of their pathophysiology and are distinct from children before the age of 12. However, this was not significant due to the small sample size, and thus, a final decisive statement cannot be established.

MMD has a complex pathology that entails an interplay between genetic, angiogenic, immune, and inflammatory factors [22, 23], and a good understanding of these factors is key to designing a treatment protocol. We previously demonstrated the value of RNF213 as a susceptibility gene for MMD [22]; however, the exact mechanisms linking RNF213 abnormalities to MMD have not yet been determined. Certain biological markers are known to be expressed in MMD, such as vascular endothelial growth factors and MMP-9 [20, 22]. We previously detected the expression of MMP-9 in MMD patients [20], and, as a consequence, introduced minocycline, an MMP-9 inhibitor, to our perioperative protocol [11]. To date, the nature of MMD is not fully understood, which leads us to adopt a policy for pediatric patients of very long-term follow-ups throughout their life because the dynamic nature of MMD may lead to delayed complications, as we reported previously, with the development of de novo AVM in one child [12, 24] or to changes in the nature of the disease from ischemic to hemorrhagic or other complications that have yet to be reported.

## Conclusion

Combined direct and indirect bypass surgery for the treatment of MMD is a safe and effective treatment. The value of the perioperative protocol cannot be stressed upon enough, and a well-designed protocol along with successful surgery results in good outcomes, as demonstrated in the present study.

We consider the protocol described herein for the treatment of MMD to be successful in counteracting most of the complications associated with the management of this disease, and the value of this protocol is reflected in the cognitive outcomes achieved over the long-term follow-up periods.

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**Compliance with ethical standards**

**Disclosure** The authors declare that they have no conflict of interest regarding the present study.

## References

1. Fujimura M, Kaneta T, Tominaga T (2008) Efficacy of superficial temporal artery-middle cerebral artery anastomosis with routine postoperative cerebral blood flow measurement during the acute stage in childhood moyamoya disease. Childs Nerv Syst 24:827–832
2. Fujimura M, Tominaga T (2015) Current status of revascularization surgery for moyamoya disease: special consideration for its 'internal carotid-external carotid (IC-EC) conversion' as the physiological reorganization system. Tohoku J Exp Med 236:45–53
3. Fujimura M, Tominaga T (2012) Lessons learned from moyamoya disease: outcome of direct/indirect revascularization surgery for 150 affected hemispheres. Neurol Med Chir (Tokyo) 52:327–332
4. Thines L, Petyt G, Aguettaz P, Bodenant M, Himpens FXX, Lenci H et al (2015) Surgical management of Moyamoya disease and syndrome: current concepts and personal experience. Rev Neurol 171:31–44
5. Hayashi T, Shirane R, Fujimura M, Tominaga T (2010) Postoperative neurological deterioration in pediatric moyamoya disease: watershed shift and hyperperfusion. J Neurosurg Pediatr 6:73–81
6. Kim S-KK, Seol HJ, Cho B-KK, Hwang Y-SS, Lee DS, Wang K-CC (2004) Moyamoya disease among young patients: its aggressive clinical course and the role of active surgical treatment. Neurosurgery 54:840
7. Bao XY, Duan L, Yang WZ, Li DS, Sun WJ, Zhang ZS et al (2015) Clinical features, surgical treatment, and long-term outcome in pediatric patients with moyamoya disease in China. Cerebrovasc Dis 39:75–81
8. Fujimura M, Kaneta T, Shimizu H, Tominaga T (2009) Cerebral ischemia owing to compression of the brain by swollen temporal muscle used for encephalo-myo-synangiosis in moyamoya disease. Neurosurg Rev 32:245–249, discussion 249
9. Fujimura M, Kaneta T, Mugikura S, Shimizu H, Tominaga T (2007) Temporary neurologic deterioration due to cerebral hyperperfusion after superficial temporal artery-middle cerebral artery anastomosis in patients with adult-onset moyamoya disease. Surg Neurol 67:273–282

10. Fujimura M, Inoue T, Shimizu H, Saito A, Mugikura S, Tominaga T (2012) Efficacy of prophylactic blood pressure lowering according to a standardized postoperative management protocol to prevent symptomatic cerebral hyperperfusion after direct revascularization surgery for moyamoya disease. Cerebrovasc Dis 33:436–445
11. Fujimura M, Niizuma K, Inoue T, Sato K, Endo H, Shimizu H et al (2014) Minocycline prevents focal neurological deterioration due to cerebral hyperperfusion after extracranial-intracranial bypass for moyamoya disease. Neurosurgery 74:163–170, discussion 170
12. Fujimura M, Kimura N, Ezura M, Niizuma K, Uenohara H, Tominaga T (2014) Development of a de novo arteriovenous malformation after bilateral revascularization surgery in a child with moyamoya disease. J Neurosurg Pediatr 13:647–649
13. Czabanka M, Vajkoczy P, Schmiedek P, Horn P (2009) Age-dependent revascularization patterns in the treatment of moyamoya disease in a European patient population. Neurosurg Focus 26:E9
14. Abla AA, Gandhoke G, Clark JC, Oppenlander ME, Velat GJ, Zabramski JM et al (2013) Surgical outcomes for moyamoya angiopathy at barrow neurological institute with comparison of adult indirect encephaloduroarteriosynangiosis bypass, adult direct superficial temporal artery-to-middle cerebral artery bypass, and pediatric bypass: 154 revascularization surgeries in 140 affected hemispheres. Neurosurgery 73:430–439
15. Choi JI, Ha SK, Lim DJ, Kim SD (2015) Differential clinical outcomes following encephaloduroarteriosynangiosis in pediatric moyamoya disease presenting with epilepsy or ischemia. Childs Nerv Syst 31:713–720
16. Phi JH, Wang KC, Cho BK, Lee MS, Lee JH, Yu KS et al (2011) Long-term social outcome in children with moyamoya disease who have reached adulthood. J Neurosurg Pediatr 8:303–309
17. Kuroda S, Houkin K, Ishikawa T, Nakayama N, Ikeda J, Ishii N et al (2004) Determinants of intellectual outcome after surgical revascularization in pediatric moyamoya disease: a multivariate analysis. Childs Nerv Syst 20:302–308
18. Shim KW, Park EK, Kim JS, Kim DS (2015) Cognitive outcome of pediatric moyamoya disease. J Korean Neurosurg Soc 57:440–444
19. Kazumata K, Ito M, Tokairin K, Ito Y, Houkin K, Nakayama N et al (2014) The frequency of postoperative stroke in moyamoya disease following combined revascularization: a single-university series and systematic review. J Neurosurg 121:432–440
20. Fujimura M, Watanabe M, Narisawa A, Shimizu H, Tominaga T (2009) Increased expression of serum matrix metalloproteinase-9 in patients with moyamoya disease. Surg Neurol 72:476–480, discussion 480
21. Guzman R, Lee M, Achrol A, Bell-Stephens T, Kelly M, Do HM et al (2009) Clinical outcome after 450 revascularization procedures for moyamoya disease. Clinical article J Neurosurg 111:927–935
22. Fujimura M, Sonobe S, Nishijima Y, Niizuma K, Sakata H, Kure S et al (2014) Genetics and biomarkers of moyamoya disease: significance of RNF213 as a susceptibility gene. J Stroke 16:65–72
23. Piao J, Wu W, Yang Z, Yu J (2015) Research progress of moyamoya disease in children. Int J Med Sci 12:566–575
24. Feroze AH, Kushkuley J, Choudhri O, Heit JJ, Steinberg GK, Do HM (2015) Development of arteriovenous fistula after revascularization bypass for moyamoya disease: case report. Neurosurgery 11(Suppl 2):E202–E206

## Comments

Motohiro Morioka, Fukuoka, Japan

Sherif Rashad et al. examined the long-term outcome of pediatric moyamoya disease (MMD) patients treated by combined direct–indirect revascularization surgery and obtained good surgical outcome. The authors emphasized the importance of combination surgical method of direct and indirect revascularization. As the authors described, the poor outcome of pediatric MMD patients is principally caused by cerebral infarction.

I agree with the authors' representation that combination therapy of direct–indirect surgery is the best treatment for pediatric patients, as the cerebral blood flow would increase immediately after surgery, if direct bypass could be performed.

I consider there are some problems in the surgical strategy for pediatric (especially very young) patients with MMD: First, in some pediatric cases, direct bypass is difficult because of fragile and small vessels in very young children, as authors discussed. If the very young patient have only one branch of STA, the failure of direct bypass would result in loss of blood flow source (for example, source of EDAS).

Second, it is unclear how to manage the case with bilateral severe CBF decrease, or the case with bilateral rapid progression of arterial stenosis. The authors did not perform bilateral revascularization surgery simultaneously (within the same day). Although it is rare, there might be the possibility that the contralateral hemisphere might suffer stroke in the time waiting for second surgery. No ischemic complications were observed during the latency period between the first and second surgeries in this study, and the authors emphasized blood pressure control and oral aspirin. However, I experienced one severe case suffered complete stroke of contralateral hemisphere 1 month after the first surgery, while she took low-dose aspirin. I considered the simultaneous bilateral revascularization surgery could prevent the contralateral stroke for this case, although blood transfusion might be necessary.

It is necessary in future to establish more certain and safe bypass procedure for small arteries and to establish the method to detect severe and rapid progressive cases

Jeong Eun Kim, Seoul, South Korea

The article describes a series of cases of pediatric moyamoya disease (MMD) operated on at a single center using combined revascularization procedures. Because of technical easiness and good revascularization outcome, simple indirect revascularization surgery is usually done for the pediatric MMD. I agree with the authors' emphasis on combined procedures for the pediatric MMD in three regards. First, some groups, especially younger ones among the pediatric MMD patients, are well known to have more aggressive progression. In those patients, hemodynamic compensation should be too urgent for the indirect revascularization to meet the need. Second, the direct procedures, including superficial temporal artery-to-middle cerebral artery bypass, are very challenging for the vessels with smaller caliber in the pediatric patients. However, the neurovascular surgeons who are skilled at the STA-MCA bypass for the adult MMD patients can sufficiently cope with that kind of technical challenge after experiencing the learning curve for the procedures. Moreover, indirect procedure can act as insurance in the case of failure of direct procedures. Third, the main critique for the direct procedures in the MMD patients is that the direct one shows more complication, such as hyperperfusion syndrome, than the indirect one. The authors well describe how to deal with and reduce the potential risk of surgical complications after combined revascularization.

The weaknesses are the small number of the enrolled patients with wide range of age (2 to 16 years), which confounds the effects of combined procedures. In spite of such flaws, this work is very thoughtful and presents a good option for the pediatric MMD patients along with traditional techniques.

Akitsugu Kawashima, Chiba, Japan

The authors demonstrate experience with combined direct and indirect bypass surgery for pediatric cases of moyamoya disease with their perioperative management. This manuscript demonstrates low surgical complication rate and long-term excellent outcome. I agree with authors' argument that there are difference features of moyamoya disease between in childhood (before the age of 12) and in adolescent (between the ages of

12 and 16). Cases of moyamoya disease in childhood were more complicated than were the cases in adolescent in the points of present symptoms and postoperative complications. They also described that adolescent cases of moyamoya disease are similar to adults in terms of their pathophysiology. The authors' view is almost the same as our 60 cases of pediatric cases of moyamoya disease. A further study of features of pediatric moyamoya disease in the point of view of ages should be conducted. I believe the manuscript is interesting and useful contribution for neurosurgeon engaged in treatment of moyamoya disease as detail of surgical and perioperative management.