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Effect of Revascularization on Headache Associated with Moyamoya Disease in Pediatric Patients

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ABSTRACT

Episodic headache is common in childhood moyamoya disease (MMD). The onset, mechanism, cause of headache and the effect of revascularization surgery on headache are not yet clear. We studied 10 cases of children (7 boys and 3 girls) younger than 18 years who underwent revascularization for MMD between 2009 and 2013. We evaluated frequency of headache and cerebral blood flow changes by single photon emission computed tomography brain imaging with [I123]-labeled iofetamine (IMP-SPECT) before and after surgery. Patients' ages ranged from 0 to 15 years at onset and 2 to 17 years at the time of surgery, mean age being 6.7 and 8.0 years respectively. 9 of 10 patients presented with ischemic symptoms and 8 had headache. 5 patients underwent indirect bypass and 5 underwent combined direct and indirect bypass. Cerebral blood flow improvement was obtained in 14 of the 15 cerebral hemispheres revascularized. The mean follow-up duration was 32.9 months. All the patients had good outcomes with improvement of ischemic neurological deficits. Headache improved in 7 (87.5%) of 8 patients. Headache in pediatric moyamoya disease is associated with change in cerebral hemodynamics. Revascularization including combined direct bypass and indirect techniques may be required to reduce headache in patients with MMD.

Key words: *Moyamoya disease, Headache, Cerebral revascularization, Pediatric*

Moyamoya disease (MMD) is characterized by the progressive occlusion of the internal carotid artery or its terminal branches with spontaneous development of a collateral vascular network[4,15,20)]. MMD has two age distribution peaks at around 5 and 40 years and is predominant in females. In children, the clinical presentation of MMD disease usually includes repeated transient ischemic attacks (TIAs) or seizures whereas adults present with intracranial hemorrhage usually in basal ganglia. The incidence of the disease in Japan is between 0.54-0.94/100,000/year[1,21)]. Outside of Japan, the incidence is about one-tenth of that seen in the Japanese population[2,3,6,10,18)].

The goal of surgical intervention in MMD is to improve blood flow to hypoperfused cerebrovascular territories, and includes direct and indirect revascularization[16)]. Direct revascularization is the procedure of choice of many authors over indirect revascularization whenever possible[7,12)]. The long-term outcome in patients who have undergone direct revascularization as a treatment of MMD was satisfactory with regard to activities of daily living (ADL)[14)]. Patients with MMD often complain of headache before and/or after surgery. However, the actual pathophysiology of headache before and after surgical treatment has not yet been clarified. We performed a retrospective analysis on ten pediatric cases of MMD who underwent revascularization surgery and herein present their clinical characteristics and outcomes after revascularization surgery, with special reference to headache.

METHODS

From 2009 to 2013, 10 patients (7 boys and 3 girls) younger than 18 years with MMD were treated at the Department of Neurosurgery, Kagoshima University Hospital. Thorough chart review of the patients' data including the clinical features, investigations, surgical procedures and follow-up was

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performed. All the patients underwent neurological examination, computed tomography (CT) and/or magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), transcranial Doppler sonography (TCD), four-vessel digital subtraction angiography (DSA) and N-isopropyl-*p*-[^{123}I]iodoamphetamine single-photon emission computed tomography (IMP-SPECT) before surgery.

Surgery was usually performed initially in the symptomatic and hemodynamically affected hemisphere. Combined direct (superficial temporal artery and middle cerebral artery cortical branch (STA-MCA) bypass) and/or indirect cerebral revascularization (encephalo-duro-arterio-myo-synangiosis (EDAMS) or encephalo-duro-arterio-myo-periosteal-synangiosis (EDAMPS) methods) were employed. In four patients who underwent bilateral revascularization, surgery was performed on the contralateral hemisphere within one month of the initial revascularization. In cases with signs of bilateral hypoperfusion on IMP-SPECT, surgery was opted for the side with more severe involvement and responsible for the neurological deficit in the patient. Follow-up MRA was performed to check the development of collaterals and IMP-SPECT was obtained to evaluate the change in cerebral hemodynamics. If headache disturbed daily activities, required rest and/or medication, and occurred at least once a month, it was considered to be significant. We excluded the pain related to surgery.

This retrospective study was approved by the ethical committee of Kagoshima University Graduate School of Medical and Dental Sciences (reference No. 505).

RESULTS

(Table 1 and Table 2)

Patients' ages ranged from 0 to 15 years at onset and 2 to 17 years at the time of surgery, mean age being 6.7 and 8.0 years respectively. 9 of a total 10 patients had clinical presentation of brain ischemia, including numbness and weakness of extremities. 8 patients had headache, with associated vomiting in 6 cases. MRA revealed stenotic arteries and IMP-SPECT demonstrated hemodynamic abnormalities with signs of hypoperfusion in all cases.

Table 1. Clinical and SPECT features of the patients

Case	Age (y) /sex	Age at surgery (y)	Neurological deficit	Headache	Vomiting	Hypoperfusion area on SPECT	
						Right	Left
1	0/F	2	Weakness of left upper limb and right upper and lower limbs	(–)	(–)	ACA/MCA/ PCA	MCA
2	2/M	3	Weakness of right upper limb	(–)	(–)	(–)	MCA
3	4/M	4	Weakness of left upper and lower limbs, cataplectic attack with crying	(+)	(+)	MCA	ACA/MCA
4	4/M	6	Weakness of both lower limbs, fall attack	(+)	(+)	ACA/MCA	MCA
5	6/M	7	Weakness right upper limb, fall attack	(+)	(+)	(–)	ACA/MCA
6	8/M	8	Impaired consciousness, involuntary movements of left upper limb	(+)	(+)	MCA	(–)
7	6/M	8	Weakness and numbness of left upper limb	(+)	(+)	MCA	ACA/MCA
8	10/M	11	Left arm weakness	(+)	(–)	ACA/MCA	ACA/MCA
9	12/F	14	(–)	(+)	(+)	(–)	MCA
10	15/F	17	Involuntary movements of the extremities, weakness of left side of body	(+)	(–)	ACA/MCA	ACA/MCA

SPECT: single photon emission computed tomography; ACA: anterior cerebral artery; MCA: middle cerebral artery; PCA: posterior cerebral artery

Table 2. Operation and postoperative outcome of the patients

Case	Revascularization procedure	Improvement on postoperative SPECT	Improvement of headache postoperatively
1	B/L EDAMPS	(+)	*
2	Lt EDAMPS	(+)	*
3	Rt STA-MCA bypass & EDAMPS	(+)	(+)
4	B/L STA-MCA bypass & EDAMPS	(+)	(+)
5	B/L EDAMPS	(+)	(+)
6	Rt EDAS	(–)	(–)
7	Rt STA-MCA bypass & EDAMS; After 2 years, Lt STA-MCA bypass & EDAMS	(+)	(+)
8	Rt STA-MCA bypass & EDAMS	(+)	(+)
9	Lt EDAMS	(+)	(+)
10	B/L STA-MCA bypass & EDAMS	(+)	(+)

Rt: right; Lt: left; B/L: bilateral; EDAS: encephalo-duro-arterio-synangiosis; EDAMPS: encephalo-duro-arterio-myo-periosteal-synangiosis; EDAMS: encephalo-duro-arterio-myo-synangiosis; STA: superficial temporal artery; MCA: middle cerebral artery; *: Headache was not present preoperatively

All the patients underwent revascularization surgery. Direct revascularization (STA-MCA bypass) combined with indirect (EDAMS or EDAMPS) was performed in 5 cases and indirect revascularization alone was performed in 5 cases. Bilateral procedures were performed in four cases: combined direct and indirect methods in two and indirect alone in two. There were no major postoperative complications.

The mean follow-up period was 32.9 months (range: 7-60 months). Ischemic neurological deficits improved in all the patients. Postoperative headache was found in only 12.5% (1 of 8) of the patients with preoperative headache and there was no case of postoperative headache in the patients without preoperative headache. One patient with persistent postoperative headache (Case 6) was found to have no improvement of blood flow on postoperative SPECT although his neurological deficit improved after encephalo-duro-arterio-synangiosis (EDAS). The other 9 patients showed an improvement in cerebral perfusion on postoperative IMP-SPECT. One patient (Case 7) presented with contralateral symptoms of neurological deficit two years after the surgery and underwent reoperation (combined left STA-MCA bypass and EDAMPS), with improvement of the deficit postoperatively.

ILLUSTRATIVE CASES

Case 3

A 4-year-old boy was brought to our hospital with crying associated with cataplectic attacks involving the left upper and lower limbs on a weekly basis. There was also a history of morning headache and vomiting. Fluid attenuated inversion recovery (FLAIR) (Fig. 1a) and T2-weighted MRI showed infarction in the right fronto-parietal region (Fig. 1b). MRA (Fig. 1c) and DSA (Fig. 1d) showed severe stenosis of the right MCA with compromised distal blood flow, and mild stenosis of the left anterior cerebral artery (ACA) and the left MCA with intact distal blood flow. The findings of hypoperfusion on IMP-SPECT accorded with infarction areas on MRI (Fig. 1e). Right STA-MCA bypass (Fig. 2a) along with EDAMPS was performed. Near infrared indocyanine green (ICG) videoangiography during surgery confirmed the patency of STA-MCA anastomosis (Fig. 2b). The dura mater, temporal muscle, and frontal pericranium were used as the donor tissues for indirect bypass. The postoperative course was uneventful. Postoperative MRA showed well-developed collaterals through both the direct and indirect bypass (Fig. 2c). IMP-SPECT also revealed improved cerebral blood flow on the right side (Fig. 2d). Headache and other neurological symptoms disappeared after surgery.

Case 6

An 8-year-old boy presented with a chief complaint of headache and vomiting every morning, general malaise, and loss of consciousness while playing the pianica in a music class with a cataplectic attack involving the left upper limb. MRA and DSA showed mild stenosis of right MCA with intact distal blood flow (Fig. 3a & 3c). IMP-SPECT at rest showed hypoperfusion in the right cerebral hemisphere compared with the contralateral side and corresponded with the stenotic area on MRA (Fig. 3b). Indirect cerebral revascularization (right EDAS) was performed. Post-operative MRA did not show significant collateral development (Fig. 4a) and IMP-SPECT did not reveal any remarkable improvement in cerebral blood flow on the right side (Fig. 4b). Postoperatively, the neurological deficit improved but headache has been persistent and he has been on regular follow-up.

DISCUSSION

Childhood MMD mainly presents as symptoms of cerebral ischemia with repeated transient ischemic attacks or seizures whereas adults mainly present with intracranial hemorrhage. While it is unclear whether adult MMD represents a progression from the juvenile form, one theory suggests that the bleeding in adults occurs from the breakdown of collateral vessels formed at a younger age[8].

Headache is one of the commonest symptoms of moyamoya disease, especially in children[9,17,22]. Seol et al reported that headache was documented in 44 (21.6%) of 204 pediatric patients with moyamoya disease. They also described the clinical course of headache in pediatric moyamoya disease as having the following features: (i) a coexisting stage of headache and TIA; (ii) the second stage of headache only; and (iii) the final stage of improvement or disappearance of headache[17]. Kawabori et al reported that headache attack was seen in 11 (38%) of 29 pediatric patients[9]. Headache was the most common presenting symptom in 40% of 10 children presenting with MMD in a report by Yamashiro et al[22]. An epidemiological study of MMD in Taiwan by Hung et al documented that headache was present in about 49% of the patients[6]. 44% of 96 pediatric patients presented with headache in a large series of a total 450 patients by Guzman R et al[5]. According to Matsushima et al, the majority of headaches were localized in the frontal (40%) or temporal region (25%) and headache affected ADL in about 60% of the patients[13]. In our study, headache was present in 80% (8 of 10) of the patients and was associated with vomiting in 60% (6 of 10).

The pathophysiological mechanism of headache in MMD remains unclear, but it has been suggested that dilatation of the meningeal collaterals stimu-

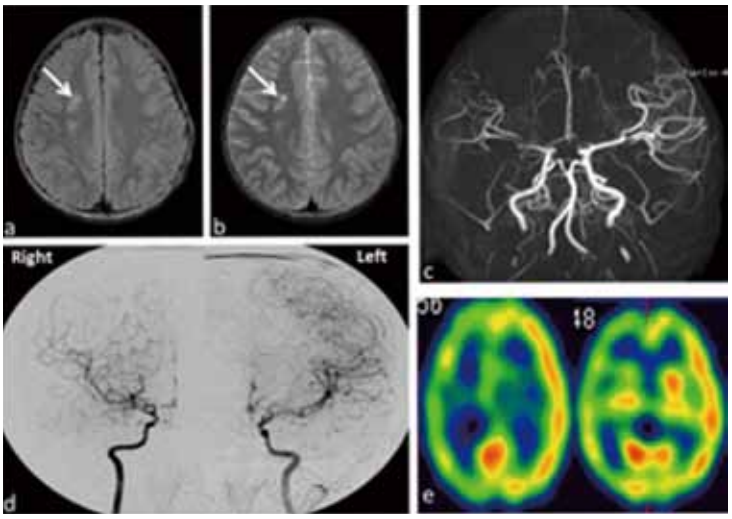

Fig. 1. Preoperative radiological findings of Case 3. (a) Fluid attenuated inversion recovery (FLAIR) and (b) T2-weighted magnetic resonance imaging (MRI) showed infarction in right fronto-parietal region. (c) Magnetic resonance angiography (MRA) and (d) digital subtraction angiography (DSA) showed severe stenosis of right MCA with compromised distal blood flow, and mild stenosis of left anterior cerebral artery (ACA) and left MCA with intact distal blood flow. (e) N-isopropyl-*p*-[^{123}I]iodoamphetamine single-photon emission computed tomography (IMP-SPECT) at rest demonstrated the findings of hypoperfusion in the areas corresponding with infarction areas on MRI.

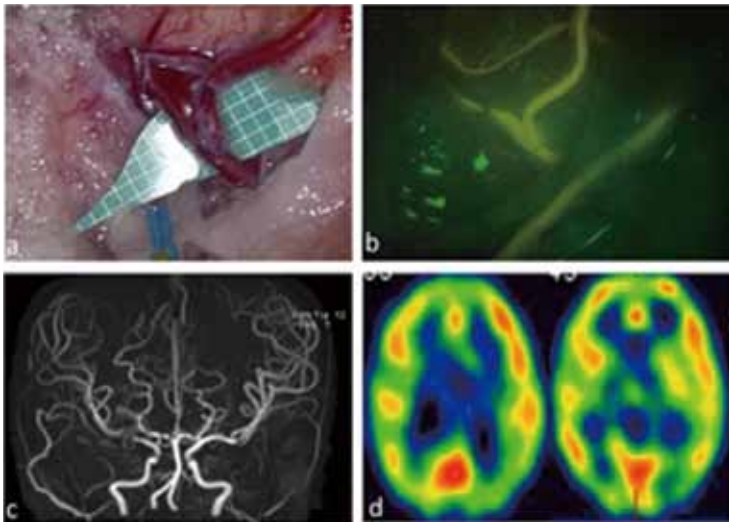

Fig. 2. Intraoperative and postoperative findings of Case 3.
Intraoperative pictures showing (a) right superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis and (b) near infrared indocyanine green (ICG) videoangiography confirming the patency of STA-MCA anastomosis. (c) Postoperative magnetic resonance imaging (MRA) showed well developed collaterals through both direct and indirect bypass. (d) Postoperative N-isopropyl-*p*-[^{123}I]iodoamphetamine single-photon emission computed tomography (IMP-SPECT) at rest revealed improved cerebral blood flow in the right cerebral hemisphere.

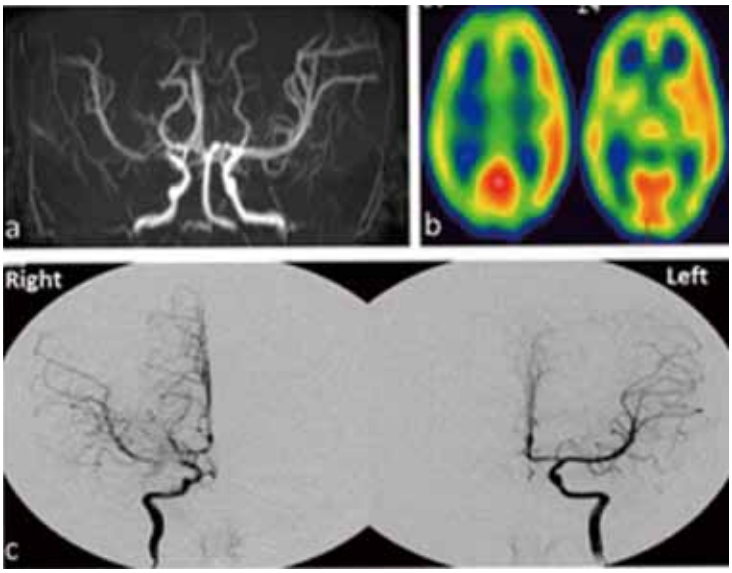

Fig. 3. Preoperative radiological findings of Case 6. (a) Magnetic resonance angiography (MRA) showed mild stenosis of right MCA with intact distal blood flow. (b) N-isopropyl-*p*-[^{123}I]iodoamphetamine single-photon emission computed tomography (IMP-SPECT) at rest showed hypoperfusion in the right cerebral hemisphere compared to the contralateral side. (c) Digital subtraction angiography (DSA) demonstrated mild stenosis of right MCA with intact distal blood flow.

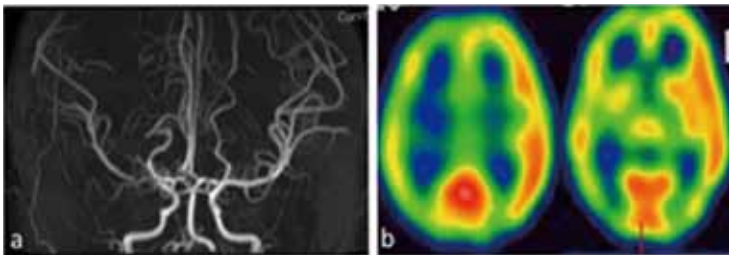

Fig. 4. Postoperative radiological findings of Case 6. (a) Post-operative magnetic resonance angiography (MRA) did not show significant collateral development. (b) N-isopropyl-*p*-[^{123}I]iodoamphetamine single-photon emission computed tomography (IMP-SPECT) did not reveal any remarkable improvement in cerebral blood flow on the right side.

lating dural nociceptors could contribute to it[19]. Ischemia-induced lowering of the migraine threshold has also been speculated as the possible underlying mechanism[17]. Headache in MMD is presumed to be closely related with hypoperfusion because revascularization has been reported to improve headache in many cases. Many techniques of revascularization have been developed. The first direct revascularization STA-MCA (extracranial-intracranial) anastomosis for MMD was performed by M. G. Yasargil and Y. Yonekawa in 1972[23]. Kawabori et al reported that headache improved in all their 11 pediatric patients with MMD who underwent combined STA-MCA bypass and EDAMPS[9]. Matsushima et al reported that headache improved or disappeared in about 75% of pediatric patients after EDAS[13]. Seol et al, however, showed that headache persisted in more than 60% of their patients even after EDAS[17]. In our study, revascularization improved headache in 7 (87.5%) of 8 patients. Patients' neurological conditions, severity of obliteration of cerebral arteries on CA, and cerebral hypoperfusion demonstrated on SPECT were our main criteria for cerebral revascularization surgery. In one patient (Case 6) with persistent headache, only unilateral indirect technique (EDAS) had been performed, which might not have been sufficient to revascularize the ischemic area, as was also indicated by the lack of remarkable improvement in blood flow on postoperative IMP-SPECT examination. As the patient had generalized headache, hemispheric ischemia visible on MRA and SPECT may not have been sufficient by itself to explain the cause of his generalized headache. Although in general the region of headache is supposed to correspond with the hypoperfusion area, generalized non-localized headache has been reported in about 50% of patients with ischemic attacks[11]. The ischemia-induced lowering of the migraine threshold[17] could be a possible contributory factor for persistent generalized headache in such patients and the persistence of generalized headache in case 6 can also be attributed to this mechanism.

Indirect bypass induces spontaneous angiogenesis between the vascularized donor tissue and the brain surface and has been considered to function well in most pediatric patients with MMD. However, the procedure is performed via temporoparietal craniotomy and the revascularization is confined to that area. It has been reported that indirect techniques may not be sufficient to improve hemodynamics in the frontal lobe[7,9,12], which is the most common location of headache in patients with MMD[13]. Hence, direct techniques combined with indirect might play a vital role in improving headache in pediatric patients with MMD.

In our study, there was no patient without preoperative headache who experienced postoperative headache. However, newly developed postoperative headache in MMD has been reported in the literature. The mechanism of newly developed headache after surgery in MMD is not yet clear. Kawabori et al documented that 1 (5.5%) out of 18 patients without preoperative headache started a headache after surgery[9]. Seol et al reported that 10 (6.3%) of 160 patients without preoperative headache developed postoperative headache and speculated that the dilation of some collateral vessels may progress even after surgery giving rise to newly developed or recurrent headaches[17]. Further research is necessary to elucidate the exact mechanisms of headache, either preoperative or postoperative, in MMD.

The most important limitation of this study is the small number of patients and our study also carries the limitations inherent in a study of a retrospective nature. Furthermore, we presented a single institutional experience, making these results difficult to generalize. Nevertheless, this study demonstrates that revascularization improves neurological deficits and headache in most of the children with MMD and that direct combined with indirect techniques might be more important for wider revascularization, especially in patients with headache.

CONCLUSION

Headache in pediatric MMD seems to be associated with disturbance in cerebral hemodynamics. Revascularization surgery in patients with MMD carries a low risk, and is effective for preventing future ischemic events including headache. Combined direct bypass and indirect techniques are preferable to indirect techniques alone to revascularize a wider area with cerebral ischemia, especially in patients with headache. Inclusion of a greater number of patients and further longitudinal follow-up will help to deduce more definitive conclusions in future.

Conflicts of Interest Disclosure

The authors declare that there is no conflict of interest regarding the publication of this paper.

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