Effective Surgical Revascularization Improves Cerebral Hemodynamics and Resolves Headache in Pediatric Moyamoya Disease

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Abstract

Objective: Headache is one of major clinical presentations in pediatric moyamoya disease. However, the clinical features and underlying mechanisms are not fully understood. This study aimed to clarify the clinical feature of headache in pediatric moyamoya disease and the effect of surgical revascularization.

Methods: This study included 29 pediatric patients who underwent superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis and indirect bypass for moyamoya disease. Their medical records were precisely evaluated to identify clinical features of their headache. The findings on MRI, SPECT, and PET were also analyzed.

Results: Preoperative headache was documented in 11 (38%) of 29 patients. Majority of them complained of severe headache in the frontal or temporal region in the morning. Headache was significantly related to more advanced disease stage and to the decreases in cerebral blood flow and its reactivity to acetazolamide. Surgical revascularization completely resolved headache in all 11 patients.

Conclusion: These findings strongly suggest that disturbed cerebral hemodynamics may play key roles to develop severe headache in pediatric moyamoya disease. STA-MCA anastomosis and EDMAPS may be effective procedures to rapidly resolve their headache by widely supplying collateral blood flow to the operated hemispheres.

(192 words)

Keywords:
Headache, moyamoya disease, bypass surgery, cerebral hemodynamics
INTRODUCTION

Moyamoya disease is an uncommon cerebrovascular disease that is characterized by progressive steno-occlusion of the supraclinoid internal carotid artery and its main branches within the circle of Willis. This occlusion results in the formation of a fine vascular network (the moyamoya vessels) at the base of the brain. Clinical presentations of moyamoya disease are very unique. Most children with moyamoya disease develop transient ischemic attack (TIA) or cerebral infarction, whereas about half of adult patients develop intracranial bleeding, and other half develop TIA or cerebral infarct (11). On the other hands, headache is one of the serious symptoms associated with moyamoya disease, especially in pediatric patients. Typically, they present with migraine-like severe headache in the frontal area in the morning. They cannot go to their school because of severe headache. Headache is often associated with vomiting and spontaneously resolves within several hours (1, 23, 27, 30, 35). Migraine-like headache is also observed in some of adult patients with moyamoya disease (27, 31, 35). According to previous studies, persistent cerebral ischemia may be closely related to the occurrence of headache in pediatric moyamoya disease, because surgical revascularization may improve or resolve it (30). However, there are almost no studies that denote the relationship between cerebral hemodynamics and headache in pediatric patients with moyamoya disease. Therefore, the authors believe that it is quite important to explore the underlying mechanism in order to establish more effective treatment and improve their quality of life.

Based on these considerations, this study was aimed to clarify the role of cerebral hemodynamics in their headache and to survey the effects of surgical revascularization on headache in pediatric moyamoya disease.
PATIENTS AND METHODS

Patients

This study included totally 29 pediatric patients who were admitted due to moyamoya disease and underwent surgical revascularization at Hokkaido University Hospital between 1997 and 2010. All of them were Japanese and met the guidelines for the diagnosis criteria of the Research Committee on Moyamoya Disease of the Ministry of Health, Labor, and Welfare of Japan. There were 7 boys and 22 girls. Their age ranged from 5 to 17 years with a mean age of 10.0 years.

Prior to surgery, the frequency, timing, region and severity of headache were precisely evaluated in all patients. Based on functional impairment, severity of headache was classified into three categories: 1) mild, patient is aware of a headache but is able to continue daily routine with minimal alteration; 2) moderate, the headache inhibits daily activities but is no incapacitating; 3) severe, the headache is incapacitating; and 4) status, a severe headache that has lasted more than 72 hours (4).

Radiological Examinations

Prior to surgery, all patients underwent precise neuroradiological examinations, including magnetic resonance (MR) imaging, MR angiography, and cerebral angiography. Disease stage was classified into 6 stages according to Suzuki’s angiographical stage (33). Using $^{133}$xenon or $^{123}$I-IMP single photon emission tomography (SPECT) or $^{15}$O-gas positron emission tomography (PET), cerebral blood flow (CBF) before and after intravenous injection of 10-mg/kg acetazolamide was quantitatively measured, as reported previously (12, 15-18). In this study, the involved hemisphere was considered as the candidate for surgical revascularization when having impaired reactivity to acetazolamide
Cerebrovascular reactivity (CVR) to acetazolamide was determined as follows: 

$$\text{CVR} (%) = 100 \times \frac{\text{CBF}_{ACZ} - \text{CBF}_{\text{rest}}}{\text{CBF}_{\text{rest}}}$$ 

where \( \text{CBF}_{\text{rest}} \) and \( \text{CBF}_{ACZ} \) represent CBF before and after intravenous injection of acetazolamide, respectively. As normal CBF value dramatically changes with growth in children, CBF was rated as reduced when the value was lower than 80% of the cerebellum in each patient (9, 16, 26). CVR was rated as reduced when it was lower than 14% (17).

**Surgical Procedures**

The patients underwent superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis and encephalo-duro-myo-arterio-pericranial synangiosis (EDMAPS) for surgical revascularization, as described before (13, 28). Briefly, the skin incision was made along the course of the parietal branch of the STA and extended upward to the midline near the bregma and then along the midline downward to the hairline. The parietal branch of the STA was dissected from the surrounding tissues, being kept patent and the point where the STA crosses the skin incision. After the scalp flap was reflected laterally, the frontal branch of the STA was also dissected under a surgical microscope. The temporal muscle was dissected as widely as possible and was made as a vascularized flap. Then, the vascularized frontal pericranium was also dissected. A standard fronto-temporal craniotomy was made, preserving the middle meningeal artery (MMA). The size of craniotomy was matched to that of the temporal muscle flap. Then, a medial frontal craniotomy was made separately, which should fit the size of the pericranial flap. The dura was incised, preserving the main branches of the MMA. Subsequently, STA-MCA single or double anastomosis was performed in an end-to-side fashion with 10-0 or 11-0 nylon threads. The frontal branches of the MCA were usually used as the
recipients of anastomoses, because cerebral hemodynamics are impaired, especially in the frontal lobe, in moyamoya disease. The clamping time of recipient was about 20 min. Then, the dural flaps were turned into the epiarachnoid space in order to make indirect bypass. The dural opening through fronto-temporal craniotomy was covered with the temporal muscle flap. The dural opening through medial frontal craniotomy was covered with the frontal pericranial flap. Cranioplasty was performed for both craniotomies, and the wound was closed. Total operation time ranged from 5 to 7 hours. No blood transfusion was performed.

Follow-up

Following surgical revascularization, all patients were followed up in the outpatient clinic. The mean follow-up period was 85.3 ± 45.7 months, ranging from 3 month to 162 month. Episodes of TIA, cerebral infarction, and intracranial hemorrhage as well as the clinical features of headache during follow-up periods were precisely recorded. Overall clinical outcomes were classified into four categories: 1) excellent, where preoperative symptoms (such as TIA) had totally disappeared without fixed neurological deficits; 2) good, where symptoms had totally disappeared but neurological deficits remained; 3) fair, where symptoms persisted, albeit less frequently; and 4) poor, where the symptoms remained either unchanged or worsened (20).

Cerebral angiography and blood flow study were repeated 3 to 6 months after surgery. Both MR imaging and MR angiography were performed every 6 or 12 months with a 1.5-T whole-body magnetic resonance imager.
Statistical Analysis
Continuous variables were expressed as mean ± standard deviation (SD). Statistical analysis was performed using Chi-square test and Kruskal-Wallis test as appropriate. The statistical level of significance was set at P<0.05.

RESULTS
Clinical Results
STA-MCA anastomosis and EDMAPS were performed on totally 50 hemispheres of 29 patients. Perioperative ischemic stroke occurred in 3 (6.0%) of these 50 surgical procedures. Cerebral infarct developed in the ipsilateral hemisphere in two patients and in the contralateral hemisphere in another. However, their neurological sequelae completely disappeared within 30 days after surgery.

During follow-up periods, TIA completely disappeared in all but one patient. Only a 7-year-old girl continued to develop transient weakness of the bilateral legs for 1 year after surgery, although its frequency decreased markedly. No ischemic or hemorrhagic stroke occurred in 29 patients during follow-up periods. Therefore, clinical outcome was categorized as excellent in 26 patients (89.7%) and good in 3 (10.3%). Three patients categorized as good outcome had mild neurological sequelae due to their initial ischemic stroke, but were independent in their ordinary life.

Clinical Features of Preoperative Headache
Prior to surgery, headache was observed in 11 (37.9%) of 29 patients. Their clinical data are shown in Table 1. Their clinical diagnosis was TIA in 10 patients and ischemic stroke in one. The frequency of headache widely varied: once everyday in two patients (18%), a
few times per week in 6 (54%), and a few time per month in 3 (27%). Headache developed in the morning in 9 (81.8%) of 11 patients and during hyperventilation such as exercising in one (9.1%). The timing of headache could not be defined in another (9.1%). Severity of headache was graded as severe in all 11 patients, because they could not go to school or kindergarten during headache attack. Nausea and vomiting were often associated with headache. Abdominal pain was simultaneously observed in one patient. Their headache could be localized in the bilateral frontal area in 3 patients (27.3%), the frontal area in 5 (45.5%), and the temporal area in 3 (27.3%). Headache spontaneously resolved within 3 to 4 hours after the onset in all 11 patients (Fig. 1).

Preoperative demographic and radiological data were precisely evaluated between 11 patients with headache and 18 patients without. There were no significant differences in age, gender, and clinical diagnosis between them (Table 2). As the next step, the relationships between headache and cerebral hemodynamics were assessed between 14 hemispheres with headache and 44 without (Table 2). As the results, Suzuki’s angiographical stage in the hemispheres with headache was significantly more advanced than in those without (P=0.029). Furthermore, a decreased CBF (P<0.01) and impaired CVR (P=0.028) were significant predictors for headache. Localization of headache closely correlated with the area with disturbed cerebral hemodynamics in all 11 patients.

**Surgical Effects on Headache**

Surgical effects on headache in each patient are shown in Table 1. Headache completely disappeared in all 11 patients within two weeks after surgery. They did not complain of headache during follow-up periods. Postoperative cerebral angiography revealed that surgical collaterals supplied blood flow to the areas where headache was repeated before
surgery. Follow-up SPECT/PET also demonstrated that both CBF and CVR normalized or improved in the operated hemispheres, including the area where they complained of headache before surgery (Table 1).

Of 18 patients without headache prior to surgery, 17 did not complain of headache after surgery. However, a 5-year-old boy developed severe headache on the right side after surgical revascularization on both sides. He often repeated severe headache, although postoperative examinations revealed a marked improvement of both CBF and CVR.

**Illustrative Cases**

**Case 7**

A 7-year-old girl experienced transient weakness of the left extremities and severe right frontal headache. She often complained of severe headache when she woke up in the morning. Magnetic resonance (MR) imaging revealed no cerebral infarction (Fig. 2A). MR angiography and cerebral angiography demonstrated severe stenosis of the terminal portion of the ICA and marked development of moyamoya vessels on the right side, defined as Suzuki’s stage 3. The lesion was less pronounced on the left side, defined as Suzuki’s stage 2 (Fig. 2B). On $^{15}$O-gas PET, both CBF and CVR were reduced in the right cerebral hemisphere, especially in the right frontal lobe where she complained of headache (Fig. 2C).

She underwent STA-MCA anastomosis and EDMAPS on the right side. Postoperative course was uneventful. Following surgery, she has experiences neither TIA nor headache. Follow-up examinations were repeated 4 month after surgery. Both CBF and CVR almost normalized on $^{123}$I-IMP SPECT (Fig. 2D). On cerebral angiography,
surgical collaterals widely supplied blood flow to the operated hemisphere, including the frontal lobes (Fig. 2E).

**Case 8**

A 12-year-old boy had complained of right frontal headache and involuntary movement of the left arm since he was 5 years old. His headache gradually increased in severity and frequency, and he was admitted to our hospital. MR imaging demonstrated small cerebral infarct in the right frontal lobe (Fig. 3A). Cerebral angiography demonstrated severe stenosis of the terminal portion of the ICA and marked development of moyamoya vessels on both sides, defined as Suzuki’s stage 3. On $^{133}$Xe SPECT, both CBF and CVR were reduced in the right frontal lobe where he often complained of headache (Fig. 3B). He underwent STA-MCA anastomosis and EDMAPS on the right side. Postoperative course was uneventful, and he became free from headache and involuntary movement.

However, he started to complain of severe headache in the left frontal area 4 months after the first operation. The patient could not go to school because of severe headache. MR imaging demonstrated the development of cerebral infarction in the left caudate head and putamen (Fig. 3C). MR angiography showed progression of disease stage in the left side. Repeated $^{133}$Xe SPECT revealed that surgical revascularization almost normalized cerebral hemodynamics in the right frontal lobe, but both CBF and CVR markedly deteriorated in the left frontal lobe (Fig. 3D). Therefore, STA-MCA anastomosis and EDMAPS were performed on the left side. Headache attack completely disappeared after the second surgery. Follow-up $^{123}$I-IMP SPECT demonstrated normalization of cerebral hemodynamics on both sides (Fig. 3E). Cerebral angiography also showed well-developed surgical collaterals in the operated hemispheres, including the
bilateral frontal lobes.

**DISCUSSION**

This study clearly explores the new aspects on headache in pediatric moyamoya disease. Thus, about 40% of pediatric patients with moyamoya disease complain of headache before surgery. Although the frequency widely varies among patients, most of them complain of severe morning headache in the frontal area. Headache spontaneously resolves within 3 to 4 hours. The hemispheres with headache have more advanced disease stage. The incidence of reduced CBF and CVR is significantly higher in the hemispheres with headache than in those without. The location of headache correlates very well with the area with disturbed cerebral hemodynamics. STA-MCA anastomosis and EDMAPS completely resolves headache in all patients who complained of it prior to surgery. This is the first report that denotes the close relationship between headache and cerebral hemodynamics in pediatric patients with moyamoya disease.

**Clinical Features of Headache in Pediatric Moyamoya Disease**

As described above, there are a limited number of studies that precisely analyzed clinical feature of headache in pediatric moyamoya disease. The incidence of headache in pediatric moyamoya disease widely varied among previous studies, probably because of different methods of survey and different definition of headache. Matsushima et al. have precisely reported its clinical feature. Thus, 47 (34.3%) of 137 pediatric patients complained of headache at initial diagnosis. A morning headache was recorded in more than 60%. Headache significantly affected their activity of daily life in more than 60%. Headache was localized in the frontal region in 40% and in the temporal region in 25%.
Headache spontaneously resolved within one hour in 25%, within 2 to 3 hr in 22%, and within 4 to 5 hr in 25% (24). Recently, Seol et al. also reported that headache was described in 44 (21.6%) of 204 pediatric patients with moyamoya disease prior to surgery. A morning headache was observed in 14 patients. However, headache could be localized in only five patients (two frontal, one parietal, and two temporal) (30).

Type of headache in pediatric moyamoya disease can often be categorized into migraine-like headache with or without an aura (1, 19, 24, 30) and hemiplegic migraine (2). However, the underlying mechanisms are still unknown. Park-Matsumoto et al. reported a 49-year-old woman who developed severe migraine with an aura due to moyamoya disease. Brain CT scans revealed cerebral infarction in the left occipital lobe. They speculated that borderline perfusion of occipital lobe cortex could be a trigger for the development of migraine with aura-like headache in susceptible patients, although it is unclear whether their hypothesis can be adapted to pediatric moyamoya disease or not (27). The present study precisely analyzed the clinical data of pediatric patients with or without headache. As the results, no significant differences in age, gender, and clinical diagnosis were observed between them. However, their disease stage was significantly more advanced in the hemispheres with headache than in those without, although the difference was very small (3.2 ± 0.4 and 2.6 ± 1.1, respectively). More importantly, a decreased CBF and impaired CVR were closely related to their headache. Therefore, persistent cerebral ischemia may be one of powerful inducers of headache attack in pediatric moyamoya disease. In fact, as presented in illustrative cases, the localization of headache was closely associated with the area with disturbed cerebral hemodynamics in all 11 patients. However, other factors would be involved in the development of their headache, because many of the patients without headache also have disturbed cerebral hemodynamics.
Further study would be necessary to fully understand the precise mechanism of headache in pediatric moyamoya disease.

**Effects of Surgical Revascularization on Headache in Pediatric Moyamoya Disease**

In this study, postoperative courses in the subjects strongly support the involvement of cerebral hemodynamics in the development of headache in pediatric moyamoya disease. Thus, STA-MCA anastomosis and EDMAPS normalized or significantly improved both CBF and CVR in the operated hemispheres, as reported previously (13). The beneficial effects on cerebral hemodynamics could widely be observed in the operated hemispheres, including the frontal lobe. Following surgery, headache completely resolved in all 11 patients (Table 1). Especially, clinical course of Case 8 is quite interesting when considering the underlying mechanism of headache in pediatric moyamoya disease. Thus, he complained of severe headache in the right forehead at onset. Blood flow measurements revealed a disturbed cerebral hemodynamics in the right frontal lobe. STA-MCA anastomosis and EDMAPS on the right side improved cerebral hemodynamics and completely resolved his headache. However, the progression of disease stage in the left side leaded to a marked reduction of cerebral perfusion pressure in the left frontal lobe, causing frequent headache in the left forehead. Additional surgery on the left side also normalized cerebral hemodynamics in the left frontal lobe and resolved his headache (Fig. 3).

Previously, Matsushima et al have also reported the beneficial effect of surgical revascularization on headache in pediatric moyamoya disease (25). Subsequently, they also reported that headache improved or completely disappeared in 75% of pediatric patients after indirect bypass procedure, encephalo-duro-arterio-synangiosis (EDAS) (22).
Seol et al. recently surveyed their clinical data after EDAS and found that postoperative headache was observed in more than 60% of the patients with preoperative headache (30). Therefore, there is a significant difference in postoperative improvement of headache between the present and previous studies. The discrepancy may result from the difference in surgical procedures. Thus, the majority of patients in these previous studies underwent bilateral EDAS (22, 25, 30). Indirect bypass surgery induces spontaneous angiogenesis between the brain surface and the vascularized donor tissues and is known to function well in most of pediatric patients with moyamoya disease. The procedures are technically easy and can even be performed by surgeons with little experience with moyamoya disease. According to a recent review by Fung et al., indirect bypass procedures have been performed in about 75% of patients in 57 studies that includes 1448 surgically treated patients between 1966 and 2004 (3). However, indirect bypass such as EDAS is performed through temporoparietal craniotomy and the revascularized area is confined to the craniotomy area. Thus, EDAS is useful to resolve ischemic attacks such as hemiparesis because surgical collaterals develop in and around the primary cortex after surgery. As pointed out by several investigators, however, the procedures do not improve disturbed cerebral hemodynamics in the frontal lobe even after surgery (8, 10, 12-14, 21, 29, 34). Considering the high incidence of frontal headache in pediatric moyamoya disease, it is most likely that many of pediatric patients still suffered headache due to impaired cerebral hemodynamics in the frontal lobe after EDAS. In fact, we have developed STA-MCA anastomosis and EDMAPS by extending the exposure of the brain surface to the medial frontal area and covering the brain surface with the vascularized pericranial flap. As the results, postoperative angiography revealed that surgical collaterals supply blood flow to the frontal lobe very widely. Blood flow studies also
showed significant improvement of cerebral hemodynamics in both the MCA and ACA territories after surgery (13). Therefore, STA-MCA anastomosis and indirect bypass through large frontotemporal craniotomy may play a critical role in resolving headache after surgery in pediatric moyamoya disease. Very recently, Shirane and Fujimura reported that STA-MCA anastomosis and indirect bypass markedly improved headache in 11 (84.6%) of 13 patients with moyamoya disease (32).

In addition, the present study demonstrated that headache resolved within two weeks after STA-MCA anastomosis and EDMAPS. However, previous study concluded that EDAS required a mean period of about two months to resolve headache after surgery (24, 25). Direct STA-MCA anastomosis may explain the difference between two studies. Thus, direct bypass procedure may be technically challenging in some pediatric patients because their cortical branches have a smaller caliber and more fragile than those of adults. However, direct bypass is useful to improve cerebral hemodynamics, reduce the incidence of perioperative complications, and resolve ischemic attacks immediately after surgery (5, 8, 13). On the other hands, indirect bypass requires 3 to 4 months to develop surgical collaterals (6, 7). Therefore, direct STA-MCA anastomosis may improve or resolve headache as well as ischemic attacks more promptly.

**Postoperative Headache in Pediatric Moyamoya Disease**

In this study, surgical revascularization completely resolved headache in 11 patients who complained of headache before surgery. However, one of 18 patients without preoperative headache started to experience headache after surgery. Blood flow measurements demonstrated that he had normal CBF and CVR after surgery. Indeed, newly developed headache after surgery has been reported previously. Thus, Matsushima
et al. reported two patients who started to develop headache attack after EDAS, although they did not complain of it before surgery (22). Seol et al. also reported that postoperative headache was observed in 10 (6.3%) of 160 patients without preoperative headache after EDAS (30). These facts strongly indicate that headache in pediatric moyamoya disease may partly occur through the mechanisms other than cerebral ischemia. Further study would be warranted to fully explore the mechanism of postoperative headache in pediatric moyamoya disease.

**CONCLUSION**

This study clearly demonstrates clinical features of headache in pediatric patients with moyamoya disease. Persistent disturbance of cerebral hemodynamics may be one of powerful factors to induce their headache. STA-MCA anastomosis and EDMAPS can rapidly resolve their headache by widely supplying collateral blood flow to the operated hemispheres, including the frontal lobes. Bypass surgery should be planned to revascularize the whole area with cerebral ischemia especially in the patients who complain of headache. However, they should be carefully followed up, because a certain subgroup of patients may develop postoperative headache. Furthermore, these results should be confirmed by analyzing the data in more number of patients in the future.

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REFERENCES


Figure Legends

Fig. 1
Clinical features of headache in pediatric patients with moyamoya disease.

Fig. 2
Radiological findings of a 7-year-old girl who underwent right STA-MCA anastomosis and indirect bypass for moyamoya disease.  A. Preoperative MRI showed no parenchymal lesion.  B. Preoperative MRA showed the marked stenosis in the right carotid fork.  C. Preoperative $^{15}$O-gas PET revealed that cerebral blood flow (CBF) and its reactivity to acetazolamide (ACZ) were reduced in the right cerebral hemisphere, especially in the right frontal lobe.  D. Postoperative $^{123}$I-IMP SPECT performed 4 months after surgery showed the normalization of CBF before and after ACZ injection.  E. Postoperative right external carotid angiogram demonstrated that surgical collaterals widely supplied blood flow to the operated hemisphere, including the frontal lobes.

Fig. 3
Radiological findings of a 12-year-old boy who complained of right frontal headache and involuntary movement of the left arm. His headache gradually increased in severity and frequency, and he was admitted to our hospital.  A. Preoperative MRI demonstrated small cerebral infarct in the right frontal lobe.  B. Preoperative $^{133}$Xe SPECT showed that cerebral blood flow (CBF) and its reactivity to acetazolamide (ACZ) were reduced in the right frontal lobe (arrows). He underwent right STA-MCA anastomosis and indirect bypass. He became free from headache and involuntary movement. However, he started to complain of severe headache in the left frontal area 4 months after the first
operation. C. Follow-up MRI demonstrated the development of cerebral infarction in the left caudate head and putamen. D. Follow-up $^{133}$Xe SPECT revealed that bypass surgery markedly improved cerebral hemodynamics in the right frontal lobe, but both CBF and its reactivity to ACZ markedly deteriorated in the left frontal lobe (arrows). Therefore, he underwent left STA-MCA anastomosis and indirect bypass. Headache attack completely disappeared after the second surgery. E. Follow-up $^{123}$I-IMP SPECT demonstrated normalization of cerebral hemodynamics on both sides.