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Symptomatic hyperperfusion after combined revascularization surgery in patients with pediatric moyamoya disease: patient series

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BACKGROUND Symptomatic hyperperfusion after cerebral revascularization for pediatric moyamoya disease (MMD) is a rare phenomenon. The authors report a series of patients with this condition.

OBSERVATIONS In all three patients in this case series, the combined revascularization was on the left side, the patency of bypass grafts was confirmed after surgery, and focal hyperemia around the anastomotic site was observed on single photon emission computed tomography (SPECT). On the first to eighth days after surgery, all of the patients developed neurological manifestations, including motor aphasia, cheiro-oral syndrome, motor weakness of their right upper limbs, and severe headaches. These symptoms disappeared completely approximately 2 weeks after surgery, and all patients were discharged from the hospital. Quantitative SPECT was performed to determine the proportional change in cerebral blood flow (ΔRCBF) (to ipsilateral cerebellar ratio (denoted ΔRCBF) in the region of interest around the anastomoses, and the mean value was 1.34 (range, 1.29–1.41).

LESSONS This rare condition, which develops soon after surgery, requires an accurate diagnosis by SPECT. One indicator is that the ΔRCBF has risen to 1.3 or higher. Subsequently, strategic blood pressure treatment and fluid management could prevent the development of hemorrhagic stroke.

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KEYWORDS combined revascularization surgery; hyperperfusion; moyamoya disease; transient neurological deficits; pediatrics

Moyamoya disease (MMD) is a rare condition that is characterized by stenotic obstructive changes at the ends of the bilateral internal carotid arteries (ICAs) and the development of basal collateral networks called moyamoya vessels (MMVs).[1,2] Direct and indirect combined revascularization surgery has been established as an effective treatment to prevent future stroke.[3–6] These surgeries consist of a superficial temporal artery (STA)-middle cerebral artery (MCA) bypass for direct bypass and the placement of vascularized pedicles using the temporal muscles, dura mater and periosteum.[7–9] It has been reported that symptomatic hyperperfusion occurs after this surgery due to the rapid inflow of blood from the direct bypass.[10–12] This condition occurs relatively frequently, especially in adult patients, and it sometimes follows hemorrhagic conversion and exacerbates the neurological outcome. Therefore,

ABBREVIATIONS ACA = anterior cerebral artery; CBF = cerebral blood flow; CBV = cerebral blood volume; COS = cheiro-oral syndrome; CT = computed tomography; CTA = computed tomography angiography; EC = external carotid; EDMPS = encephalo-duo-myo-periosteal synangiosis; ICA = internal carotid artery; MCA = middle cerebral artery; MMD = moyamoya disease; MMV = moyamoya vessels; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; PCA = posterior cerebral artery; PET = positron emission tomography; POD = postoperative day; RCBF = relative cerebral blood flow; ΔRCBF = proportional change in cerebral blood flow; ROI = region of interest; SPECT = single photon emission computed tomography; STA = superficial temporal artery; TIA = transient ischemic attack; TND = transient neurological deficits.

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numerous studies have been conducted on risk occurrence and treatment strategies.[13–16] However, postoperative symptomatic hyperperfusion rarely develops in pediatric patients with MMD and has not been investigated fully. Here, we describe three cases of pediatric patients with MMD who had specific neurological symptoms after combined revascularization for pediatric MMD, including postoperative courses and treatment strategies.

Study Description

From May 2020 to July 2021, three pediatric patients with MMD who underwent surgery at our hospital were retrospectively identified. MMD was diagnosed by magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) based on the current guidelines.[17] In all three of the patients, surgery was indicated based on the guidelines, and direct and indirect combined revascularization was performed. In this study, data were also extracted from four patients who underwent left-sided combined surgery to compare the characteristics of patients who were postoperatively asymptomatic during the same period with those of the symptomatic cases. The main procedure that was used for direct bypass was the STA-MCA single bypass. The STA graft was harvested by the cut-down technique, and an end-to-side anastomosis was performed on the MCA as a recipient. At our institution, indirect revascularization involves placing the pedicled temporal muscle, periosteum, and galea on the brain surface and suturing them with the inverted dura mater. Encephaloarteriosynangiosis using STA grafts was not performed. In combined revascularization, both the direct and indirect methods were enforced. This surgical technique, which is used in our facility, was described in a previous report.[7,18] In postoperative imaging, we evaluated the hemorrhagic complications and bypass patency with computed tomography (CT)/computed tomography angiography (CTA) on postoperative day (POD) 1. MRI/MRA was performed on POD 2 to confirm the presence or absence of ischemic stroke and bypass patency. Single photon emission tomography (SPECT), an assessment of cerebral blood flow (CBF), was performed on POD 3. At our facility, ^{99m}Tc-ethyl cysteinate dimer is used as a radioisotope for pediatric patients. Brain perfusion SPECT studies were performed using a double-head gamma camera (Symbia T or Symbia T6, Siemens Healthcare, Erlangen, Germany). CBF was quantitatively measured by manually defining a 1-cm diameter region of interest (ROI) in the exact vascular territory supplied by the bypass and the ipsilateral cerebellar hemisphere according to a previously reported method (Fig. 1).[19] For the ROI supplied by the bypass, we calculated the radioactivity count divided by the count of the ipsilateral cerebellar ROI. This value was defined as the relative cerebral blood flow (RCBF). The proportional change in the RCBF (denoted ΔRCBF) within each ROI before surgery and on POD 3 was calculated by dividing the postoperative RCBF by the preoperative RCBF. In addition, the patients underwent CT and MRI/MRA examinations according to their symptoms.

All patients were managed based on previously reported standardized postoperative management protocols.[20–23] Postoperative transient neurological deficits (TNDs) were defined as follows: (1) objectively observed reversible neurological symptoms (e.g., motor weakness, dysarthria, and aphasia); (2) reversible neurological symptoms that were subjectively reported by the patient (e.g., limb numbness); and (3) no signs of acute stroke on imaging.

MRI/MRA studies were performed for imaging follow-up 3 to 6 months after surgery, and any new stroke events and revascularization effects were evaluated.

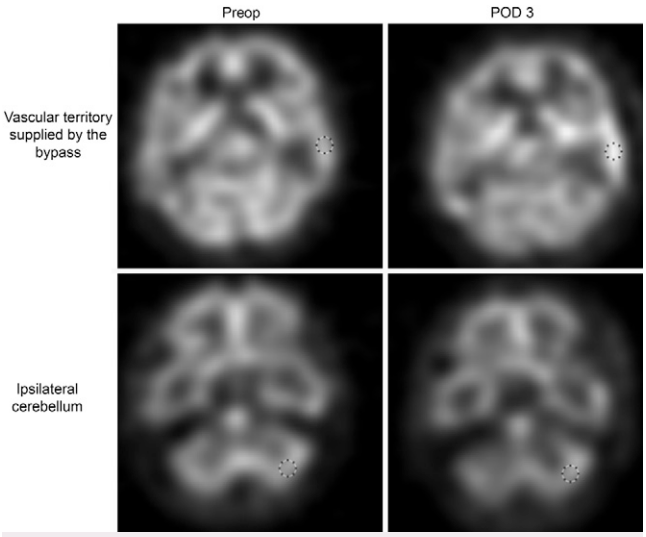

FIG. 1. Original SPECT images that were taken preoperatively and 3 days after surgery (POD 3). CBF was quantitatively measured by manually defining a 1-cm diameter ROI in the exact vascular territory supplied by the bypass and the ipsilateral cerebellar hemisphere (*dotted circle*). For the ROI that was supplied from the bypass, we calculated the radioactivity count divided by that count of the ipsilateral cerebellar ROI. This value was defined as the RCBF. The proportional change in the RCBF (denoted ΔRCBF) within each ROI before surgery and on POD 3 was calculated by dividing the postoperative RCBF by the preoperative RCBF.

Table 1 summarizes the characteristics of the three pediatric MMD patients who presented with postoperative symptomatic hyperperfusion (case 1–3) and the four patients who were postoperatively asymptomatic (case 4–7).

Case 1

A 12-year-old right-handed girl had transient motor weakness in her left upper limbs. The patient was referred to us for surgical treatment with a diagnosis of MMD. No stroke lesions were found on MRI (Fig. 2A, left). On MRA, the bilateral ICA was highly stenotic at the terminal portion, and the anterior cerebral artery (ACA) and MCA had disappeared (Fig. 2A, right). The MMVs were bilaterally developed, and the posterior cerebral artery (PCA) was not affected.

First, right combined revascularization was performed with an uneventful postoperative course. A left STA-MCA bypass and encephalo-duo-myo-periosteal synangiosis (EDMPS) were performed with any neurological abnormalities just after the surgery. From POD 2, the patient developed a severe headache, cheiro-oral syndrome (COS) on her right side, and motor aphasia, and she was crying.[24] On MRI, a sulcal hyperintensity signal appeared mainly around the anastomotic site on fluid-attenuated inversion recovery (Fig. 2B, left, red dotted ellipse). MRA allowed visualization of the STA graft (Fig. 2B, right, white arrow). On SPECT performed on POD 3, findings of focal hyperemia were observed around the anastomotic site, and the patient was diagnosed with symptomatic hyperperfusion (Fig. 2C, yellow circle). The calculated ΔRCBF was 1.41 (Table 2). The symptoms disappeared by POD 8, and the patient was discharged without any neurological abnormalities. Three months after the operation, MRA showed that a vascular

TABLE 1. Characteristics of the pediatric patients with MMD with postoperative symptomatic hyperperfusion compared to asymptomatic cases

Case No.	Age (yrs)	Sex	Type of Onset	Cerebral Infarct at Onset	PCA Involvement on Op Side	Suzuki Stage	Surgical Side	Type of Revasc	Bypass Patency	Hyperemia on SPECT	Symptoms of HP	Duration of HPS (POD)	Postoperative Stroke
1	12	F	TIA	–	–	3	Lt	Combined	+	+	Severe HA, rt COS, Motor aphasia	2–7	–
2	9	M	HA	–	–	3	Lt	Combined	+	+	Severe HA, rt COS, Motor aphasia	2–8	–
3	10	M	TIA	–	–	3	Lt	Combined	+	+	Severe HA, rt hand motor weakness, motor aphasia	1–8	–
4	7	M	TIA	+	–	3	Lt	Combined	+	–	–	–	–
5	10	F	TIA	–	–	3	Lt	Combined	+	–	–	–	–
6	12	M	HA	–	–	3	Lt	Combined	+	–	–	–	–
7	4	F	TIA	–	+	4	Lt	Combined	+	–	–	–	–

+ = positive; HP = hyperperfusion; HPS = hyperperfusion syndrome; HA = headache; Op = operative; Revasc = revascularization.

channel from the external carotid (EC) system had developed and that the MMVs on the patient's left side had regressed (Fig. 3, left). No new stroke was found on MRI (Fig. 3, right). The patient's transient ischemic attacks (TIAs) had disappeared.

Case 2

A 9-year-old right-handed boy with MMD developed a headache attack. The patient was diagnosed with MMD by MRI/MRA and referred to us for surgical treatment. Right cerebral revascularization was first performed without any postoperative events. Approximately 5 months after surgery on the right side, left STA-MCA bypass plus EDMPS was performed. Up to POD 1, the patient had no neurological abnormalities, and the bypass was visualized on CTA. From POD 2, the patient presented with right-sided COS and motor aphasia with crying and severe headache. No new stroke was observed on MRI, and the STA graft was visualized on MRA. SPECT on POD 3 showed focal hyperemia around the anastomotic site, so the patient was diagnosed with symptomatic hyperperfusion. The calculated ΔRCBF was 1.29 (Table 2). These symptoms disappeared by POD 8. Three months after the operation, no new stroke was observed on MRI. In MRA, revascularization from the EC system was strongly observed.

Case 3

A right-handed 10-year-old boy developed transient motor weakness in the left upper limbs after crying, and MMD was diagnosed by MRI/MRA. Right STA-MCA bypass plus EDMPS was performed with an uneventful postoperative course. After the first surgery, transient motor weakness of the right limbs appeared. On MRA, stenosis of the left MCA was found to be progressing; therefore, left STA-MCA single bypass plus EDMPS was performed. The bypass was visualized by CTA on POD 1. From that day, along with severe headache, motor weakness on the right hand and aphasia appeared, accompanied by crying and restlessness. SPECT on POD 3 confirmed the findings of focal hyperemia in the left frontoparietal lobe, which was recognized as symptomatic hyperperfusion. The calculated ΔRCBF was 1.32 (Table 2). Symptoms persisted until POD 8 and completely disappeared thereafter. Three months after the operation, the patient had no new stroke events on MRI. On MRA, the revascularization effect of the ECA system was moderate.

Discussion

Observations

We report three pediatric patients with MMD with specific symptoms after combined revascularization. A relatively large number of adult patients with MMD have experienced symptomatic hyperperfusion after a direct bypass.[10,14,15,25,26] However, there have been few reports that have described the common characteristic symptoms in pediatric patients with MMD.[15,27,28] Furthermore, this is the first time that ΔRCBF was verified in detail from SPECT findings of a pediatric patient with MMD during the presence of symptomatic hyperperfusion and compared with that of asymptomatic patients. In all three cases, the patients had a favorable course without the development of a new stroke after surgery. Our postoperative treatment strategies will be discussed later, and this report will provide useful information for neurosurgeons and healthcare professionals who are treating pediatric patients with MMD.

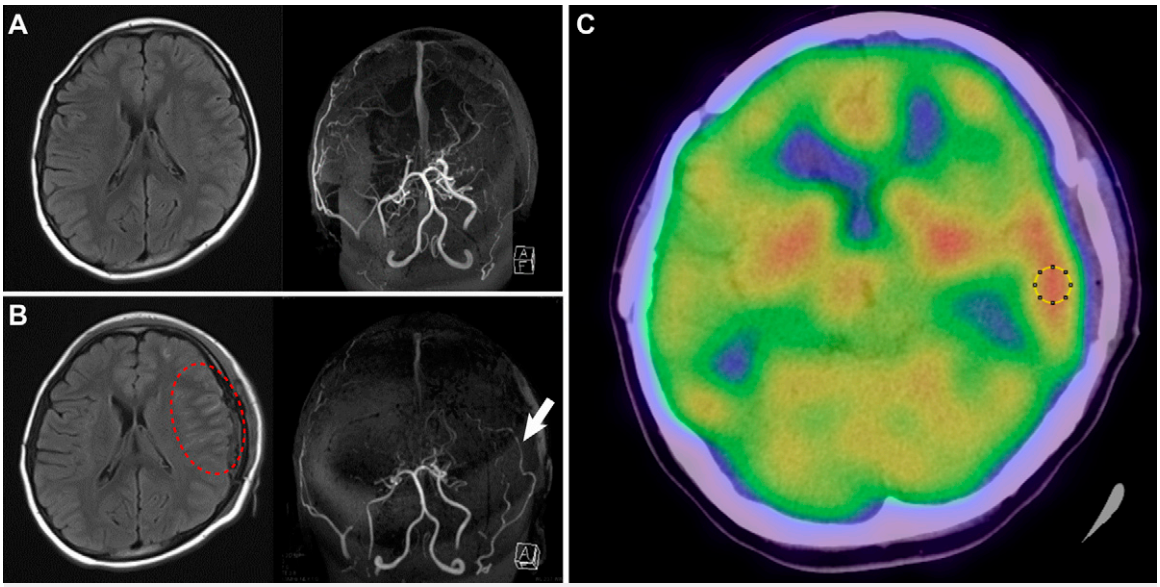

FIG. 2. Symptomatic hyperperfusion after left combined revascularization in a 12-year-old patient with MMD. **A:** No stroke lesions were found on MRI (*left*). On MRA, the bilateral internal carotid artery was highly stenotic at the terminal portion, and the ACA and MCA had disappeared (*right*). MMVs were bilaterally developed, and the PCA was not affected. **B:** On fluid-attenuated inversion recovery MRI, no new stroke events had occurred, but a sulcal hyperintensity signal had appeared, mainly around the anastomotic site in the frontal lobe (*left, red dotted ellipse*). An MRA showed an apparent visualization of the STA graft (*right, white arrow*). **C:** On SPECT performed on POD 3, findings of focal hyperemia were observed on the left frontotemporal lobe, and the patient was diagnosed with symptomatic hyperperfusion (*yellow circle*).

One of the characteristics of the symptomatic hyperperfusion of the three pediatric MMD cases we experienced was left-sided surgery. There are few reports on postoperative symptomatic hyperperfusion or TNDs in left-sided surgery, and most of them were adult patients.[15,29] Uchino et al.[15] first showed that the incidence of symptomatic hyperperfusion was significantly higher among adults (31.5%) than among children (5%). They noted that the risk factor for radiological and symptomatic hyperperfusion in adult MMD was an increase in the preoperative cerebral blood volume (CBV), as assessed using positron emission tomography (PET). The preoperative onset type and the decrease in CBF were not significant factors. Although the PET study is available only at a limited number of centers, a large-scale investigation of parameters other than the CBF, including the CBV, in pediatric MMD may shed light on the factors that contribute to this characteristic postoperative condition. On the other hand, the occurrence of symptomatic hyperperfusion in their series occurred on the left side in 10 of 13 hemispheres (76.9%) after surgery, and the same proportion of patients had a high rate of symptoms that were related to language function, such as aphasia and dysarthria. Although there are differences in age between adult and pediatric cases, it was noteworthy that aphasia appeared in all of the patients in our series. On the other hand, in the investigation by Lu et al.[29] of the prediction of postoperative TNDs, left-sided surgery was a significant

TABLE 2. Proportional changes in focal CBF before and after surgery in this study

	Preoperative		Postoperative			
Case No.	Vascular Territory Supplied by Bypass	Ipsilateral Cerebellum	Vascular Territory Supplied by Bypass	Ipsilateral Cerebellum	Focal CBF Increase*	ΔRCBF in This Study†
1	55.3	51.5	76.3	50.3	1.38	1.41
2	50.8	50.7	60	46.3	1.18	1.29
3	37.9	40.5	67.6	54.9	1.78	1.32
4	50.5	37	56	38.9	1.11	1.05
5	58.6	52.8	55.7	44.6	0.95	1.13
6	49.7	55.1	59.7	53.1	1.2	1.25
7	56.5	46.8	55.6	42.5	0.98	1.08

* As calculated by Tashiro et al.[19]

† For the ROI that was supplied by the bypass, we calculated the radioactivity count divided by that count of the ipsilateral cerebellar ROI. This value was defined as the RCBF. The proportional change in the RCBF (denoted ΔRCBF) within each ROI before surgery and on POD 3 was calculated by dividing the postoperative RCBF by the preoperative RCBF.

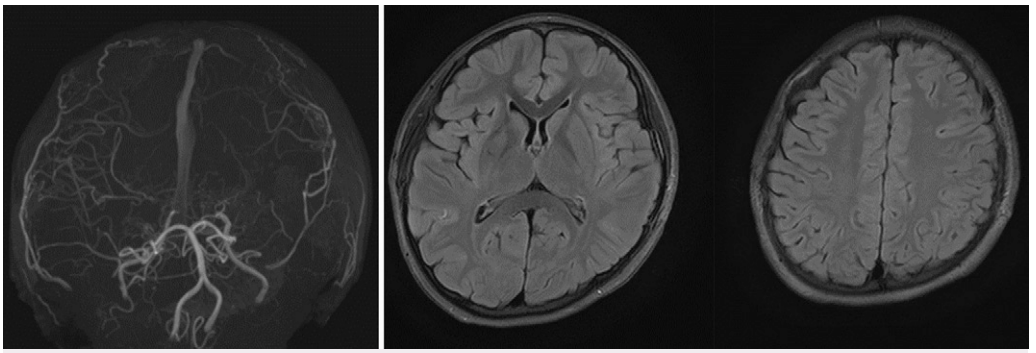

FIG. 3. MRI/MRA 3 months after revascularization. MRA showed that a vascular channel from the external carotid system had developed and that the MMVs on the left side had regressed (**left**). No new stroke was found until it developed as a chronic phase on MRI (**right**).

factor in their multivariate analysis (odds ratio, 2.9). Although their study reported only on adult patients with MMD, their findings are still important as evidence to support the occurrence of events with left-sided surgery in pediatric patients with MMD who are less likely to have postoperative symptomatic hyperperfusion. In their discussion, the verbal symptoms were present for a longer period of time than the other symptoms (mean duration 4 vs. 2 days, respectively), which was consistent with our study (mean, 7 days). We agree with the speculation that language function is susceptible to changes in CBF and is associated with revascularization. All three of our patients were right-handed, and it is expected that the dominant left hemisphere had verbal function. Therefore, the period of onset of verbal symptoms may also be prolonged. The development of COS was a characteristic nonverbal symptom in this series and was observed in two of three of the patients. According to a report from Sasamori et al.,[24] this symptom occurred transiently with a frequency of 22.9% after direct and indirect combined revascularization, and their study included one pediatric case. The duration of COS was approximately 7 days, which is similar to our report. However, they reported that no local hyperemia was observed on postoperative SPECT, concluding that COS is caused by other mechanisms. Their consideration of the MRA findings after surgery was unique. They observed preoperative and postoperative changes in the MMVs that had developed in the basal ganglia and thalamus and found that they were rapidly diminishing postoperatively. On the other hand, regarding the neurological symptoms, in a small series of cases involving COS and motor weakness, those symptoms were due to cerebral infarction of the border of the posterior limb of the internal capsule and corona radiata.[30] From that fact, it was speculated that COS in MMD patients was also due to transient blood flow disorders around the internal capsule and corona radiata.[24] Moreover, 60% of pediatric patients with MMD have been reported to begin experiencing the disappearance of MMVs 1 month after surgery, which begins within 6 months in adult patients.[31,32] Their group previously experienced a case of cerebral infarction in the ACA territory due to obstructive changes in the carotid fork due to bypass flow from the STA graft.[33] After these considerations, it was speculated that the blood flow of the internal capsule and corona radiata, which are mainly controlled by MMVs, may be impaired by the rapid conversion that is created by the direct bypass in patients with MMD. This rapid conversion from the internal carotid system to the EC system has been reported by other groups and is consistent with the watershed shift phenomenon.[27,34–36] In our case, motor weakness was observed in one of the patients, but no cerebral infarction occurred after the operation. Considering the area that is affected by the blood flow from MMVs, there is no indication that motor weakness occurs at the same time as COS, but it may be due to the difference in cerebral ischemia tolerance between children and adults. In addition, if measures against severe cerebral ischemia have not been implemented, it is possible that this patient developed a cerebral infarction.[20,22] On the other hand, the common symptom among these three patients was severe headache. A severe headache when waking up is specific to ischemic pediatric patients with MMD.[37] However, the headaches in these patients were persistent, occurring not only in the morning, but they were temporarily enhanced when the patients were restless and crying. Headaches have often been observed with postoperative hyperperfusion of adult patients with MMD, but they are rare in our experience with pediatric cases.[15] This fact convinced us that the condition in this patient was caused by clinical hyperperfusion.

In this series, we diagnosed clinical symptomatic hyperperfusion when focal hyperemia around the anastomotic site was observed on SPECT, which was performed on POD 3. In addition, we performed a quantitative SPECT assessment to investigate the radiological features of postoperative hyperperfusion, a rare condition in pediatric patients with MMD. There are many reports on the definition of postoperative hyperperfusion in adult patients with MMD. However, many of the definitions are from single-center or small-group studies, and there has not been a large-scale consensus. Some studies have calculated the percentage increase in the focal CBF before and after surgery,[11,34,38] while other studies have considered only the ipsilateral cerebellar ratio (RCBF) $>$ 150% to be important after surgery.[15] Furthermore, other studies have considered a contralateral ratio $>$ 100% to be important.[26,39] Of these various definitions of radiological hyperperfusion, we adopted a new methodology that is considered to be more stable and theoretically valid than the other definitions (Table 2).[19] First, MMD is basically a bilateral obstructive disease, and the disease stages are not equal within the left and right hemispheres. Therefore, while calculating the contralateral ratio is meaningful for comparisons in individual cases, it cannot be extended to interpreting the results from the entire MMD population. Second, the problem of comparing the preoperative and postoperative quantitative values in the vascular territory supplied by the bypass is that the CBF quantitative values in the cerebellum, which should not be affected by surgery, show relatively large differences before and after surgery. This indicates that the accuracy is insufficient when comparing only the values that are around the anastomotic site. In obstructive cerebrovascular

diseases other than MMD, it is common to use the ipsilateral cerebellar ratio (RCBF) of the target territory, which is not affected by crossed cerebellar diaschisis.[15,40] Third, evaluating only the RCBF values after surgery does not take into consideration the changes from the preoperative ischemic state, and as a result, these values may not reflect the pathophysiology of hyperperfusion. Based on the above considerations, we calculated the proportional change (ΔRCBF). Although the results were obtained in three patients, a relatively stable ΔRCBF was calculated for the characteristic symptomatic hyperperfusion pathology compared with the other methodologies (range, 1.29–1.41). Moreover, the average ΔRCBF in the asymptomatic group was 1.13 (range, 1.05–1.25), which was lower than that in the symptomatic group. These data are promising and suggest that the symptoms may have been strongly associated with hyperperfusion. Furthermore, the ΔRCBF calculated by other methods for asymptomatic patients shown in Table 2 (case 4–7) was unstable (range, 0.95–1.2), as were the values for the symptomatic cases. We are convinced that this methodology can be applied not only to pediatric patients with MMD who have had direct bypass but also to adult patients. On the other hand, although the POD 3 protocol is set up at this facility, the ΔRCBF value that predicts radial hyperperfusion will change depending on the timing of the postoperative SPECT imaging (e.g., POD 0–7).

Postoperative management for this condition should be considered. Several treatment strategies for hyperperfusion occurring in adult patients with MMD have been proposed.[13,16] However, no effective method has been shown for hyperperfusion in pediatric cases. Even drugs that can be used for adults are difficult to give to pediatric patients due to a lack of evidence for their use in children. At least for the patients described in this study, the blood pressure management and fluid therapy strategy that we used were able to prevent the development of hemorrhagic stroke.[20,22,23,41] In short, the upper limit of the blood pressure is the additional 20% of the preoperative value, and the lower limit is the preoperative baseline blood pressure. The recommended amount of fluid replacement is 1 to 1.5 times the normal maintenance rate. Furthermore, the total balance between oral intake, total infusion volume and urine output should not be negative values. However, this strategy is an empirical treatment that has been utilized in a few cases, and the level of evidence is not high. Therefore, verification by accumulating a large number of case data will be needed.

Lessons

For this rare condition that develops early after surgery, an accurate diagnosis is required by observing focal hyperemia on SPECT. One indicator can be that ΔRCBF has risen to approximately 1.3 or higher. Subsequently, strict blood pressure control and fluid management could prevent the development of hemorrhagic stroke.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Araki, Mamiya, Takayanagi, Nishihori, Kato. Acquisition of data: Araki, Mamiya, Fujita, Yokoyama, Uda, Kanamori, Takayanagi, Nishihori, Nagata, Izumi, Kato. Analysis and interpretation of data: Araki, Mamiya, Takayanagi, Tanahashi, Muraoka, Kato. Drafting the article: Araki, Takayanagi. Critically revising the article: Ishii, Nishihori, Tanahashi, Izumi, Saito. Reviewed submitted version of manuscript: Yokoyama, Uda, Kanamori, Takeuchi, Tanahashi, Nagata, Nishimura, Saito. Approved the final version of the manuscript on behalf of all authors: Araki. Administrative/technical/material support: Fujita, Uda, Nishimura, Tanei, Muraoka, Kato. Study supervision: Nishihori, Tanei, Saito.

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