

Prognostic factors associated with perioperative ischemic complications in adult-onset moyamoya disease

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Abstract

Background To clarify the risk factors associated with perioperative ischemic complications in adult-onset moyamoya disease.

Material and methods The incidence and causes of perioperative ischemic complications in adult-onset moyamoya disease were retrospectively examined by reviewing 165 surgically treated adult patients. Two hundred forty-six revascularization procedures were performed in these patients. **Results** There were 19 (7.7%) perioperative ischemic complications (four infarctions with neurological sequelae and 15 reversible ischemic neurological deficits with a new lesion). The complications occurred in the initially affected hemispheres in 17 (89.4%) of the 19 ischemic complications, regardless of the side of the operation. Multiple ischemic episodes (defined as over four-symptom episodes before treatment), the presence of a preoperative low density area (LDA) on computed tomographic (CT) scanning, and a high signal intensity on diffusion-weighted magnetic resonance (MR) imaging were signifi-

cantly correlated with perioperative ischemic complications ($p < 0.05$, $p < 0.05$, and $p < 0.01$, respectively). Non-surgical hemodynamic risk factors, i.e., hypercapnia, hypocapnia, or hypotension/hypovolemia, were noted in all of the 19 cases. None of the surgical factors evaluated were associated with the complications identified.

Conclusions Avoidance of non-surgical hemodynamic risk factors as well as maintaining vital collateral vessels is essential for the prevention of perioperative hemodynamic brain damage in patients with adult-onset moyamoya disease. In addition, very close monitoring of the perioperative care of patients with preoperative multiple ischemic episodes and an LDA or high signal intensity on preoperative CT or diffusion-weighted MR imaging is extremely important.

Keywords Moyamoya disease · Ischemia · Surgery · Perioperative complications · Outcomes

Introduction

Moyamoya disease is a chronic occlusive cerebrovascular disorder of unknown origin that is characterized by progressive occlusion of the terminal portion of the internal carotid artery, bilaterally, along with an abnormal vascular network at the base of the brain [20, 21]. Moyamoya disease can be divided into two clinical entities: juvenile- and adult-onset types [5, 15, 20, 25]. Although these two types have similar angiographic findings, it is not clear whether adult-onset moyamoya disease represents an extension or continuity of the juvenile-onset form of the disease. The clinical presentation of moyamoya disease includes not only ischemic attacks in children, but also ischemic and hemorrhagic symptoms in adults [5, 15].

For patients with symptomatic moyamoya disease, revascularization surgery is performed to prevent further

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ischemic insults [3, 8, 11, 12]. Because of the disturbance of autoregulation in hypoperfusion states [8, 16], special care is necessary to prevent neurological complications during the perioperative period. Several investigators have reported that surgical treatment for adult-onset moyamoya disease is safe, with postoperative neurologic complications occurring in 1.9% to 8.8% of cases [3, 5, 8, 12, 25]. In adult cases of moyamoya disease, however, not only direct or indirect revascularization, but also evacuation of hematomas, clipping of associated aneurysms, and other surgical procedures may be necessary. Moreover, patients with moyamoya disease are vulnerable to surgical insults, even though the injury mechanism is not clear. Although not frequent, impact of perioperative ischemic complication is significant and should be avoided. However, there are few studies that have concentrated on the perioperative ischemic complication after revascularization surgery in adult-onset moyamoya disease. Therefore, we conducted a survey of the perioperative courses of 165 consecutive patients with surgically treated adult moyamoya disease to clarify the risk factors associated with perioperative ischemic complications.

Patients and methods

Patient population and data collection

We performed 246 revascularization procedures on 165 adult patients (20 years of age or more at onset) with moyamoya disease between April 1995 and March 2008. All patients had ischemic, hemorrhagic symptoms or seizures. The clinical manifestations included cerebral ischemia ($n=131$), cerebral hemorrhage ($n=32$), or seizures ($n=2$). The median age at the time of surgery was 36 (range, 20–62 years). Table 1 summarizes the clinical findings in the 165 patients.

Medical records and radiologic studies including computed tomography (CT), magnetic resonance (MR) imaging, cerebral angiography, and single-photon emission computed tomography (SPECT) were reviewed retrospectively. Evaluation of cerebral blood flow (CBF) on SPECT was performed before and 1 month after surgery using technetium-99m hexamethylpropylene amineoxime (HM-PAO). Single-photon emission computed tomography images were obtained at rest and at 15 min after intravenous injection of acetazolamide (1 g). In patients presenting with perioperative neurological deficits, diffusion-weighted MR imaging and SPECT, using technetium-99 m HM-PAO, were performed during or just after the manifestation of symptoms. All SPECT data were interpreted by a nuclear medicine doctor who did not involve the surgery. The preoperative angiographic staging was performed based on Suzuki angiographic criteria [21] (Table 2). Patients with postoperative transient ischemic

Table 1 Base-line characteristics of the 165 patients with adult moyamoya disease

Characteristics	Value
Age at onset (years)	
Median (range)	36.0 (20–62)
Female:male (ratio)	119:46 (2.6:1)
Manifestation	
Ischemia	131
Hemorrhage	32
Seizure	2
Surgical procedure	
Direct bypass with indirect procedure	4
Direct revascularization surgery	8
Indirect revascularization surgery	228
Multiple burrhole surgery	6
Operated hemispheric sides	
Bilateral	81
Unilateral	84

attacks (TIAs) without a new lesion on neuro-imaging were excluded from this study.

All patients who underwent revascularization surgery had already demonstrated seriously compromised cerebrovascular reserve capacity on SPECT studies with acetazolamide, which indicated a high risk of ensuing cerebral infarction. In this series, our basic decision policy of surgical procedures was indirect revascularization with encephaloduroarteriosynangiosis (EDAS) because the recipient vessel in a true moyamoya patient was frequently fragile or too small to anastomose, and direct revascularization might cause more frequent perioperative complications including hyperperfusion syndrome. However, direct revascularization through STA-MCA anastomosis combined with or without indirect revascularization was performed on 12 cases. We suggest the following conditions for successful revascularization surgery in moyamoya disease: infusion of the sufficient fluids during the surgery, adequate correction of anemia, and maintenance of normocapnic and normothermic conditions.

The clinical records of these 165 patients were analyzed in detail with special reference to the surgical procedures and perioperative hemodynamic conditions, such as mean arterial blood pressure (MAP), blood gas data, as well as neurological signs and neuroradiological findings. The following parameters were examined for the survey: the minimum and maximum blood pressures, minimum and maximum PaCO₂, quantity of fluid infused, and body temperature. Non-surgical hemodynamic factors were defined in the present study as hypercapnia (PaCO₂>45 torr), hypocapnia (PaCO₂<35 torr), and hypotension/hypovolemia (MAP<85% of the preoperative MAP).

Table 2 Suzuki angiographic criteria for moyamoya disease

Grade	Detailed description
I	Narrowing of carotid fork. Only the carotid fork stenosis is observed
II	Initiation of basal moyamoya vessels. All the main cerebral arteries are dilated
III	Intensification of moyamoya. Remarkable moyamoya vessels at the base of the brain. The deflection of the MCA and ACA is observed
IV	Minimization of moyamoya. The deflection of the PCA is observed
V	Reduction of moyamoya. All the main cerebral arteries missing
VI	Disappearance of moyamoya. Cerebral blood flow supplied only from ECA

ACA anterior cerebral artery, ECA external carotid artery, MCA middle cerebral artery, PCA posterior cerebral artery

Evaluation of outcome and statistic analysis

A modified Rankin scale was used to determine the neurological functional outcome [2] (Table 3). The median follow-up period for patients in this study was 73 months (range, 15–169 months). The data of the patients with perioperative ischemic complications were compared to patients without complications. The Mann–Whitney *U* test was used to analyze the differences between groups. Possible uni- and multivariate associations between predictive factors and perioperative ischemic complications were tested using Spearman rank correlation coefficients and logistic regression test. SPSS software (version 12.0, 2003; SPSS, Inc.; Chicago, IL., USA) was used throughout, and *p* values of less than 0.05 were considered statistically significant.

Results

Among the 165 adult patients with moyamoya disease (Table 1), revascularization procedures were performed in 84 patients unilaterally and in 81 patients bilaterally. Suzuki's angiographic staging of the 246 operated hemispheric sides showed the following: stage II in 22 sides, stage III in 183 sides, and stage IV in 41 sides. Operative procedures involved direct bypass surgery combined with indirect procedures in 4 sides, direct revascularization

surgery in 8 sides, indirect surgery in 228 sides, and multiple burr hole procedures in 6 sides. The procedures used for direct surgery were mainly superficial temporal artery to middle cerebral artery anastomosis. The procedures used for indirect surgery included the combination of EDAS and encephaloduroarteriomyosynangiosis. Other operative procedures performed for initial hemorrhagic events were external ventricular drainage (EVD) in eight patients and evacuation of intraparenchymal hematomas in ten patients.

Perioperative ischemic complications

Nineteen perioperative ischemic complications (four infarctions with neurological sequelae and 15 reversible ischemic neurological deficits (RIND) with a new lesion on neuroimaging studies) were observed in 19 patients. Table 4 summarizes the clinical data of the 19 patients with perioperative ischemic complications. The median age at the time of surgery was 34 (range, 21–59 years). The diagnosis of moyamoya disease in these patients was made after the identification of cerebral ischemia in 18 cases (12 infarctions and 6 TIAs) and after intraventricular hemorrhage in one case. Among the 19 adult patients with perioperative ischemic complications, revascularization procedure was performed in two patients directly and in 17 patients indirectly. Ischemic complications developed in 17 (89.4%) out of the 19 patients with initially affected

Table 3 A modified Rankin scale

Grade	Detailed description
0	Normal neurological examination for age
1	No significant disability despite the presence of neurological symptoms and/or signs
2	Mild disability but independent in the activities of daily living
3	Moderate disability requiring assistance with the activities of daily living but able to walk with or without assistance
4	Moderately severe disability and unable to walk without assistance
5	Severe disability requiring constant nursing care and attention

Table 4 Summary of 19 patients with perioperative ischemic complications

No.	Age/ sex	Manifestation	Symptomatic hemisphere	Stage ^a	Preoperative			Operation	Onset of ischemic events after surgery	Type/location of Perioperative ischemic complication	Perioperative non- surgical factor	mRS	
					Ischemic episode	LDA on CT scan	HSI on MR-DWI					Preoperative	Last F/U
1	21/F	Ischemia	Right	III	Multiple	+	+	Indirect	20 days	RIND, right frontal	Hypotension	Grade 1	Grade 2
2	32/F	Ischemia	Left	III	Two times	+	+	Indirect	Within 24 h	RIND, left parietal	Hypercapnia	Grade 0	Grade 0
3	29/F	Ischemia	Right	III	Multiple	+	+	Indirect	Within 24 h	RIND, right frontal	Hypocapnia	Grade 0	Grade 1
4	27/F	Ischemia	Right	II	Three times	+	+	Indirect	Within 24 h	RIND, right parietal	Hypocapnia	Grade 0	Grade 1
5	59/F	Ischemia	Right	III	Multiple	+	+	Indirect	Within 24 h	RIND, right temporo-parietal	Hypotension	Grade 0	Grade 1
6	42/F	Ischemia	Right	III	Multiple	-	-	Indirect	11 days	RIND, both frontal	Hypotension	Grade 0	Grade 1
7	38/F	Ischemia	Left	III	Multiple	+	+	Indirect	Within 24 h	RIND, left temporo-parietal	Hypocapnia	Grade 0	Grade 0
8	35/F	Ischemia	Left	III	Multiple	+	+	Indirect	Within 24 h	RIND, left frontal	Hypercapnia	Grade 0	Grade 2
9	27/F	Ischemia	Left	III	Multiple	-	+	Indirect	Within 24 h	RIND, left parieto-occipital	Hypocapnia/ hypotension	Grade 0	Grade 0
10	29/F	Ischemia	Left	II	Multiple	+	+	Direct	Within 24 h	Infarction, left MCA territory	Hypocapnia/ hypotension	Grade 2	Grade 3
11	29/M	Ischemia	Right	III	One time	-	+	Indirect	Within 24 h	RIND, left frontal	Hypocapnia	Grade 0	Grade 0
12	43/F	Ischemia	Left	III	Multiple	+	-	Indirect	Within 24 h	RIND, left parietal	Hypocapnia	Grade 0	Grade 0
13	33/F	Ischemia	Left	II	Multiple	-	-	Indirect	Within 24 h	RIND, left frontal	Hypercapnia	Grade 1	Grade 2
14	44/F	Ischemia	Left	III	Multiple	-	+	Indirect	9 days	Infarction, left frontal	Hypocapnia	Grade 2	Grade 4
15	31/M	Ischemia	Right	III	Multiple	+	+	Direct	Within 24 h	Infarction, right MCA territory	Hypocapnia/ hypotension	Grade 1	Grade 2
16	25/F	Ischemia	Left	III	One time	+	+	Indirect	10 days	RIND, right frontal	Hypercapnia	Grade 0	Grade 0
17	23/M	Ischemia	Left	III	Multiple	+	+	Indirect	7 days	RIND, left occipital	Hypercapnia	Grade 0	Grade 0
18	31/F	Ischemia	Left	III	Multiple	-	-	Indirect	Within 24 h	RIND, left frontal	Hypotension	Grade 0	Grade 1
19	53/F	Hemorrhage	Right	IV	Two times	+	+	Indirect	Within 24 h	Infarction, both frontal	Hypocapnia	Grade 2	Grade 3

Multiple ischemic episodes were defined as over four-symptom episodes before treatment

^a Preoperative angiographic stages were evaluated using the criteria of Suzuki angiographic stage

CT tomography, HSI high signal intensity, LDA low density area, MR-DWI magnetic resonance diffusion-weighted imaging, F female, F/U follow-up, M male, mRS modified Rankin scale, MCA middle cerebral artery, RIND reversible ischemic neurological deficit

hemispheres, regardless of the side of the operation. Angiographic staging of the 19 patients with perioperative ischemic complications revealed stage II in three sides, stage III in 15 sides, and stage IV in only one side. Onset of ischemic complications occurred between days 0 and 20 postoperatively. Among 14 (74%) of the 19 patients, ischemic complications occurred within 24 h, postoperatively. Clinical symptoms of perioperative ischemic complications varied, including motor weakness, speech disturbance, and sensory disturbance. No ischemic complications developed after non-revascularization procedures including EVD or evacuation of hematomas.

Factors associated with perioperative ischemic complications

Perioperative ischemic complications were not associated with gender, age at onset, angiographic staging, or type of operation. Multiple ischemic episodes (defined as over four-symptom episodes before treatment), the presence of a preoperative low density area (LDA) on CT scanning, and a high signal intensity on the diffusion-weighted MR imaging were significantly correlated with perioperative ischemic complications ($p < 0.05$, $p < 0.05$, and $p < 0.01$, respectively).

In all of the 19 patients, non-surgical hemodynamic risk factors were found during the perioperative period. Hypercapnia, hypocapnia, and hypotension/hypovolemia were noted in five, ten and seven patients, respectively. Table 5 shows the type of complication and these factors. There was no difference in the frequency of hemodynamic factors between the patients with and without complications; however, all four of the patients with infarction had evidence of hypocapnia.

None of the surgical factors appeared to be associated with the complications. Postoperative angiography confirmed the patency of direct bypasses in all patients except

one. However, one patient with occlusion of direct revascularization was not symptomatic.

Results of preoperative and postoperative SPECT studies

All patients who underwent revascularization surgery had already demonstrated seriously compromised CBF on SPECT studies. After surgery, evaluation of CBF on HM-PAO SPECT was performed in 105 out of 165 patients. In 78 of 90 patients without perioperative ischemic complications, CBF improved or normalized after surgery. In the remaining 12 patients, however, cerebral hemodynamics were often still impaired in the frontal lobes, even after surgery if the surgical field is confined to the temporoparietal area. Whereas the HM-PAO SPECT performed in 15 of 19 patients with perioperative ischemic complications during or just after the onset of neurological deficits, all of the results showed focal hypoperfusion (Fig. 1b).

Long-term clinical outcome

Among the 19 patients with perioperative ischemic complications, four patients had infarctions with permanent neurological sequelae, and 15 patients had RIND with functional recovery. Among the 19 patients, no patient died due to ischemic complications. At final follow-up (median, 73 months after surgery; range, 15–169 months), 16 patients (84%) were independent with regard to their functional outcome according to a modified Rankin scale (independent; grades 0, 1, and 2).

Discussion

One of the well-known specific features of moyamoya disease is its pattern of age distribution, in adults and

Table 5 Preoperative and perioperative non-surgical factors in 19 patients with perioperative ischemic complications

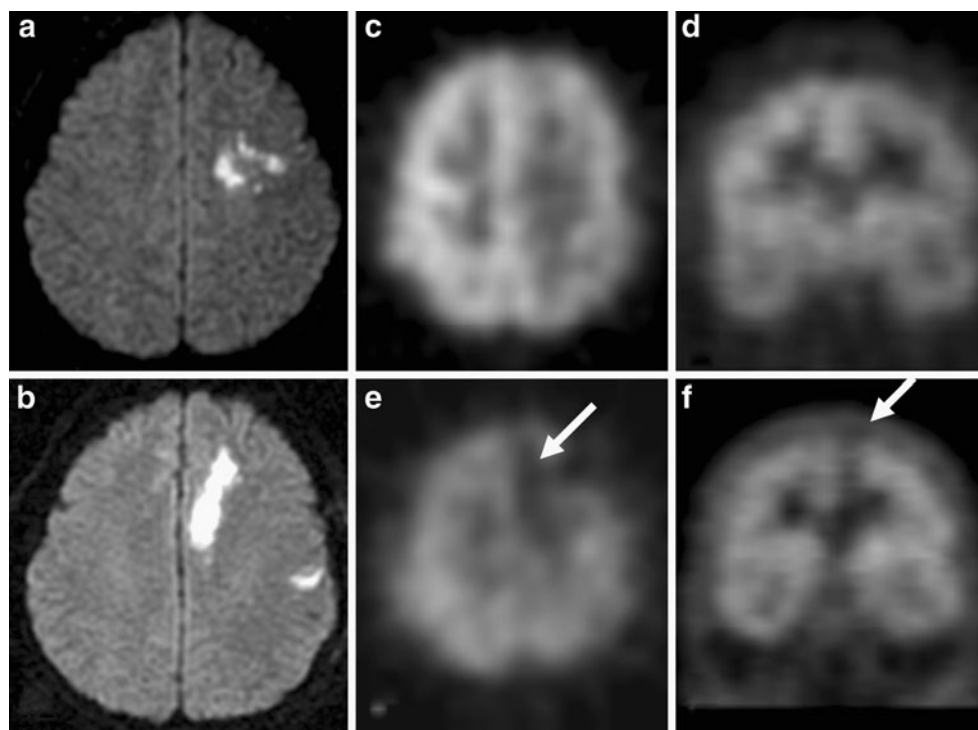
Perioperative complications	Preoperative factors (%)			Perioperative factors (%)		
	Multiple ischemic episodes ^a	LDA on CT scan ^a	HSI on MR-DWI ^a	Hypercapnia	Hypocapnia	Hypotension/hypovolemia
Yes ($n=19$)	14 (74)	13 (68)	15 (79)	5 (26)	10 (53)	7 (37)
Infarction ($n=4$)	3 (75)	3 (75)	4 (100)	0	4 (100)	2 (50)
RIND ($n=15$)	11 (73)	10 (67)	11 (73)	5 (33)	6 (40)	5 (33)
No ($n=146$)	49 (34)	51 (35)	42 (29)	51 (35)	54 (37)	36 (25)
Total ($n=165$)	64 (39)	64 (39)	57 (35)	61 (39)	74 (47)	50 (32)
p value	<0.05	<0.05	<0.01	NS	NS	NS

Multiple ischemic episodes were defined as over four-symptom episodes before treatment

^a Factors were significantly correlated with perioperative ischemic complications

CT computed tomography, HSI high signal intensity, LDA low density area, MR-DWI magnetic resonance diffusion-weighted imaging, NS not significant, RIND reversible ischemic neurological deficit

Fig. 1 A representative example of postoperative ischemic complications in a patient with adult-onset moyamoya disease: Preoperative (a) and postoperative (b) diffusion-weighted magnetic resonance (MR) images demonstrating a newly developed ischemic area in the left frontal lobe. Hexamethylpropylene amineoxime single-photon emission computed tomography image obtained preoperatively (c and d) and on day 3 postoperatively (e and f) shows an area of focal relative hypoperfusion in the left frontal lobe (arrow) corresponding to the hyperintense area on diffusion-weighted MR images



children, with a higher incidence in childhood [8, 20, 25]. However, a recent study by Baba et al. [1] revealed a higher incidence in adults, particularly in female patients, when compared to children. In fact, with recent advances in neuroradiological diagnostic modalities, including MR angiography and three-dimensional CT angiography, the diagnosis of adult-onset moyamoya has become more frequent than in the past. Thus, information regarding the management of adult-onset moyamoya disease is important. In addition, information regarding perioperative ischemic complications in adult-onset moyamoya disease can indirectly shed light on the possible pathogenesis and pathophysiology of this disorder.

Perioperative ischemic complications

Nineteen perioperative ischemic complications (7.7%, 19/246 sides) were identified in this series. Takahashi et al [22] reported that postoperative MRI demonstrated fresh areas of infraction in four (8.3%) patients, and permanent neurological deficits remained in two (4.2%) patients, including pediatric patients. However, prior reports, and the present study, suggest that almost all symptoms were temporary and completely improved [14, 17, 22]. In the current study, only four (1.6%) patients experienced infarction with permanent neurological sequelae, and 15 patients had a good functional recovery. At the final follow-up, only three patients (1.2%) had a relatively poor functional outcome with a grade 3 and 4 using a modified Rankin scale.

It is not clear whether decreased hemodynamic reserve or autoregulation affects the operative results in adult cases similar to juvenile cases. In contrast to juvenile cases, more cases of adult-onset moyamoya disease are associated with intracranial bleeding [16, 21]. However, cerebral ischemic attacks are seen less frequently in adult cases than in juvenile cases, even when they present with cerebral ischemia [10, 20, 21]. Therefore, the hemodynamic conditions of adult cases appear to be more stable than in juvenile patients. In our series, the frequency of perioperative ischemic complications was 11.5% (19/165) in adult patients, which was lower than in the juvenile patients (16.9%, 21/124) [10].

Factors associated with perioperative ischemic complications

In the current study, multiple ischemic episodes before treatment, the presence of preoperative LDA on CT scanning, and hyper-intense signals on diffusion-weighted MR imaging were significantly correlated with perioperative ischemic complications. A preoperative LDA indicated the presence of brain damage and was suggestive of advanced disease [18]. In addition, a hyperintense signal on the diffusion-weighted MR imaging suggests ongoing cerebral ischemic changes and unstable cerebral conditions. Therefore, the presence of an LDA or high signal intensity on the preoperative CT or diffusion-weighted MR imaging should be considered a sign of cerebral ischemia. Preoperative multiple events of

cerebral ischemia has also been cited as a risk factor for perioperative ischemic disorders of the cerebral circulation [6, 10, 11, 13, 18, 25]. In adult-onset moyamoya, patients that have these factors, very close monitoring of patients during the perioperative period is required because the CBF is unstable, and the vessels become atonic and lose their capacity for normal autoregulation.

Previous investigators described patients with moyamoya disease and Graves disease as being at an increased risk for cerebrovascular ischemic events [9]. Alterations of cerebral hemodynamics, vascular reactivity to the sympathetic nervous system, and cerebrovascular autoregulation in the thyrotoxic state have been mentioned as possible triggers of the cerebral ischemic attacks in moyamoya disease [9, 19]. Although there was no co-existing thyrotoxicosis in this series, further studies are required to establish the exact nature of the relationship between thyroid dysfunction and perioperative ischemic complications in moyamoya disease.

Non-surgical hemodynamic risk factors

In our series, although the statistical analysis did not clarify the relevance of such factors for ischemic complications, several hemodynamic risk factors were noted in all of the 19 patients that developed perioperative cerebral ischemia. These findings suggest that these hemodynamic risk factors might be associated with cerebral hypoperfusion in adult patients as well as in juvenile patients. Even in patients with no history of cerebral ischemic attacks, the hemodynamic vascular reserve was often reduced, as assessed by the CBF studies [13, 16, 24, 26]. Moreover, prior studies have reported the results of CBF studies with acetazolamide challenge as a useful method for evaluating the risk of perioperative complications [10, 13]. Therefore, CBF studies should be performed, to the extent possible, in all patients with moyamoya disease. However, this might be difficult in patients requiring urgent surgery for intracranial bleeding. Perioperative management maintaining normocapnia and normotension is likely to aid in the prevention of complications even in adult cases.

Perioperative cerebral ischemia versus postoperative cerebral hyperperfusion

Recently Ohue et al. [17] studied the frequency and mechanisms involved in postoperative neurological deficits in adult patients with moyamoya disease. The investigators suggested that postoperative neurological deficits were caused by cerebral hyperperfusion rather than ischemic changes. They found that focal hyperperfusion on the HM-PAO SPECT with edema or no permanent infarction on postoperative MRI. In our study, however, the HM-PAO

SPECT performed in 15 of 19 patients with perioperative ischemic complications during or just after the onset of neurological deficits; all of the results showed focal hypoperfusion. The diffusion-weighted MR was performed in all 19 patients during or just after the onset of neurological deficits; acute cerebral ischemic findings were demonstrated in all 19 cases (Fig. 1d). The postoperative cerebral perfusion status must be evaluated carefully, as treatment for hyperperfusion is opposite to that required for postoperative ischemia. If a postoperative neurological deficit is caused by postoperative hyperperfusion, systemic arterial pressure must be strictly controlled to within the normal or lower range [4, 7, 14, 17, 23, 25, 26].

Conclusions

Avoidance of non-surgical hemodynamic risk factors as well as maintaining vital collateral vessels is essential for the prevention of perioperative hemodynamic brain damage in adult-onset moyamoya disease. In addition, close perioperative management is especially important in patients with multiple ischemic episodes before treatment, an LDA or high signal intensity on the preoperative CT or diffusion-weighted MR imaging. Furthermore, perioperative ischemic complications may develop within areas where the hemodynamic reserve was initially decreased, even when revascularization has been performed.

Disclaimer None of the authors have any financial interest in the subject under discussion in this paper.

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- The authors retrospectively analyzed perioperative ischemic complications in adult-onset moyamoya disease. They showed 19 (7.7%) of 165 surgically treated adult patients who showed ischemic complications between 0 and 20 days after surgery. It is interesting and important to know that even after the indirect revascularization, ischemic complications occurred. As the authors mentioned, close observation of the patients with preoperative multiple ischemic episodes is important.
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