

## NEUROSCIENCES AND NEUROANAESTHESIA

# Predictive factors of symptomatic cerebral hyperperfusion after superficial temporal artery-middle cerebral artery anastomosis in adult patients with moyamoya disease

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### Editor's key points

- Moyamoya is a disease characterized by intimal thickening of the terminal internal carotid arteries.
- In children, symptoms are caused by ischaemia, whereas in adults, most neurological signs result from haemorrhage.
- Among 82 patients with Moyamoya undergoing extracranial to intracranial anastomoses, 29 suffered symptomatic cerebral hyperperfusion (SCH).
- Factors associated with SCH were operation on the dominant side, and a leucocytosis on the day after surgery.

**Background.** Symptomatic cerebral hyperperfusion (SCH) is a potential complication after superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis in patients with moyamoya disease. This retrospective study was designed to determine factors associated with SCH after STA-MCA anastomosis in adult moyamoya patients.

**Methods.** Eighty-two adult moyamoya patients undergoing STA-MCA anastomosis between July 2005 and December 2010 were enrolled. Laboratory data such as haemoglobin and white blood cell (WBC) count, preoperative (patient characteristic data, initial clinical manifestation, the angiographic staging), intraoperative (surgical time, the operative side, anaesthetic technique, fluid balance, arterial pressure, arterial partial pressure of carbon dioxide, the lowest haematocrit, and intraoperative transfusion), and postoperative (arterial pressure, Acute Physiology and Chronic Health Evaluation II score) data were collected and used as predictable factors for postoperative SCH, in which a focal intense increase in cerebral blood flow at the anastomosis site was shown in postoperative single-photon emission computed tomography.

**Results.** Among 82 patients with 99 surgeries, 39 patients (47 sides, 47%) suffered from transient neurological deterioration due to SCH from 1 to 9 days after operation (median: 2 days), which was sustained for 1–14 days (median: 7 days). The operation on the dominant hemisphere [odds ratio (OR), 5.09; 95% confidence interval (CI), 2.07–12.54,  $P < 0.001$ ] was an independent risk factor for SCH. Also, WBC count on postoperative day 1 was significantly correlated with SCH (OR 1.19; 95%CI, 1.02–1.38,  $P = 0.029$ ).

**Conclusions.** The operation on the dominant hemisphere and increased postoperative WBC count may be associated with SCH after STA-MCA anastomosis in adult-onset moyamoya patients.

**Keywords:** moyamoya disease; risk factor; superficial temporal artery-middle cerebral artery anastomosis; symptomatic cerebral hyperperfusion

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With regard to the treatment of adult-onset moyamoya disease, direct revascularization surgery such as superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis has become one of the standard therapeutic options.<sup>1–3</sup> Direct revascularization has been shown to significantly improve cerebral blood flow and thus potentially prevent brain infarction.<sup>4</sup> Bypass also offloads stressed moyamoya vessels, thus potentially decreasing the risk of haemorrhage. However, the incidence of postoperative transient neurological deterioration due to cerebral hyperperfusion

syndrome was reported with a range of 27–38% in patients with adult-onset moyamoya disease after the procedure.<sup>5–7</sup> Diagnosis of symptomatic cerebral hyperperfusion (SCH) is clinically important, because it has a substantial risk for haemorrhage which may lead to surgical morbidity/mortality.<sup>8,9</sup>

To our knowledge, there have been few reports concerning risk factors for SCH after direct revascularization surgery in patients with moyamoya disease. A previous study demonstrated that adult-onset and haemorrhagic-onset patients had higher risk for SCH after STA-MCA anastomosis.<sup>6</sup>

Another study revealed that postoperative neurological deficits occurred more frequently in younger patients or those with poor vascular response before surgery.<sup>7</sup> However, predictors associated with SCH after STA-MCA anastomosis remain unclear.

Thus, the aim of this study was to determine factors associated with SCH after STA-MCA anastomosis in adult patients with moyamoya disease.

## Methods

After Institutional Review Board approval, we retrospectively analysed collected data for consecutive patients with moyamoya disease, who were admitted to surgical intensive care unit (SICU) after direct extracranial–intracranial revascularization surgery for improvement of compromised cerebral circulation under general anaesthesia in Seoul National University Hospital between July 2005 and December 2010.

Patients with the treatment of only indirect extracranial–intracranial revascularization surgery were excluded. Paediatric patients were also excluded.

With respect to anaesthetic technique, the radial artery cannulation was performed under local anaesthesia before anaesthetic induction in all patients. Anaesthesia was induced with propofol (effect-site concentration: 4–6 ng ml<sup>-1</sup>) and remifentanyl (effect-site concentration: 4–6 ng ml<sup>-1</sup>) using a target-controlled infusion pump, and maintained using total i.v. anaesthesia with propofol [effect-site concentration: 4 (1) ng ml<sup>-1</sup>] and remifentanyl [effect-site concentration: 4 (2) ng ml<sup>-1</sup>] or balanced anaesthesia with sevoflurane (up to 2.5 vol%) and remifentanyl [effect-site concentration: 4 (2) ng ml<sup>-1</sup>]. Intraoperative systolic arterial pressure was strictly maintained at the level of the highest preoperative systolic arterial pressure  $\pm$  20 mm Hg until MCA-STA anastomosis was finished. If necessary, phenylephrine (20–30  $\mu$ g) was intermittently administered or continuously infused (0.5–1.0  $\mu$ g kg<sup>-1</sup> min<sup>-1</sup>) with titration to maintain systolic arterial pressure. After completion of STA-MCA anastomosis, systolic arterial pressure was kept at the level of the lowest preoperative systolic arterial pressure  $\pm$  20 mm Hg. Hyperventilation was avoided to maintain arterial  $P_{\text{CO}_2}$  between 4.7 and 6.0 kPa during the surgery. Intraoperative haemoglobin concentration was maintained at the level of minimum 10 g dl<sup>-1</sup>. All surgery was performed by one neurosurgeon. Surgical technique such as craniotomy size, STA preparation, and the site (the fourth branch of MCA) and size of anastomosis was not changed during this study period.

Before admission to SICU after the surgery, the brain computed tomography (CT) scan was routinely taken in all patients to detect surgery-related haematoma or infarction. All patients underwent complete neurological examination by neurosurgeons when they became fully awake. Mean arterial pressure was maintained strictly within 20 mm Hg difference from preoperative basal arterial pressure level for about 4 days of the postoperative period. Cerebral

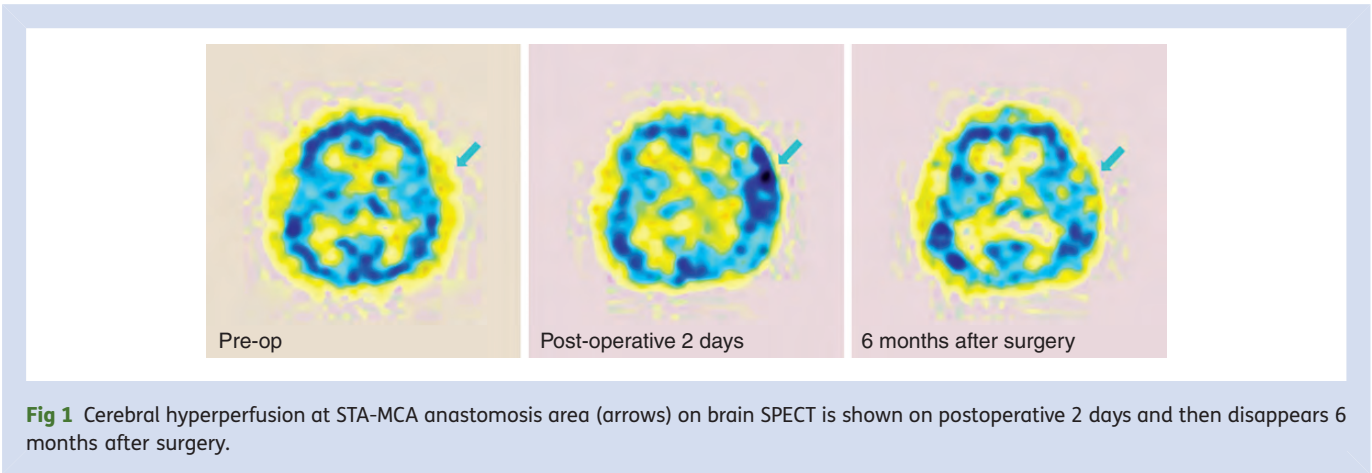
conventional angiography, magnetic resonance angiography, or both were done on the second, seventh, or 10th postoperative day to evaluate the patency of STA-MCA anastomosis and perfused area of the bypass. For the evaluation of postoperative changes in cerebral perfusion, basal and acetazolamide-challenged brain perfusion single-photon emission computed tomography (SPECT) with Tc-99m-HMPAO was taken on the second, seventh, or 10th postoperative days and compared with that before surgery.

We analysed the presence of SCH and recorded the timing of occurrence after STA-MCA anastomosis. As described in a previous report,<sup>10</sup> SCH was defined if all the following four factors were met: (i) new development of postoperative focal neurological deficits, seizure, and symptomatic subarachnoid haemorrhage which were not shown before operation and in the immediate postoperative period; (ii) postoperative reversible neurological deficits which were completely resolved within 15 days after operation; (iii) neither definite haematomas nor definite acute infarction on a brain CT scan, on diffusion magnetic resonance imaging, or both; (iv) significant focal increase in cerebral blood flow at the site of the anastomosis on postoperative SPECT (Fig. 1). Finally, a neurosurgeon, who is blinded to this study, confirmed the patients with postoperative SCH.

Medical records were reviewed retrospectively. Data on patients consisted of four parts: (i) preoperative factors including patient characteristic data, initial clinical manifestation, the highest and lowest both systolic and diastolic arterial pressures on general ward, Glasgow coma scale, the angiographic staging based on Suzuki and Takaku<sup>11</sup> angiographic criteria, significant decreased perfusion on SPECT (cerebral blood flow <50%), and laboratory findings including haemoglobin and white blood cell (WBC) count; (ii) intraoperative factors including surgical time, anaesthetic time, the operative side, anaesthetic technique (propofol–remifentanyl vs sevoflurane–remifentanyl), fluid balance during anaesthesia, the highest and lowest both systolic and diastolic arterial pressures during anaesthesia, the highest and lowest arterial carbon dioxide tensions, the lowest haematocrit, and intraoperative transfusion; (iii) postoperative factors including systolic and diastolic pressures on admission to SICU, immediate postoperative haemoglobin and WBC count, APACHE 2 score, the first postoperative day haemoglobin and WBC count; and (iv) hospital course data including hospital mortality and the length of stay in ICU and hospital.

## Data analysis

For continuous variables, values were compared using the Student *t*-test for independent samples. Differences in proportions were compared using the  $\chi^2$  or Fisher exact test where the cell size was small. Only variables with a *P*-value of <0.25 in the *t*-test or the  $\chi^2$  test were included in binary logistic regression with the forward stepwise conditional method to determine the independent risk factors for SCH. All tests were two-tailed, and a *P*-value of <0.05 was considered significant.



**Fig 1** Cerebral hyperperfusion at STA-MCA anastomosis area (arrows) on brain SPECT is shown on postoperative 2 days and then disappears 6 months after surgery.

**Table 1** Preoperative factors. Data are presented as numbers, mean (SD), or mean (range). TIA, transient ischaemic attack; SPECT, single-photon emission computed tomography; HSAP and LSAP, the highest and lowest systolic arterial pressure; HDAP and LDAP, the highest and lowest diastolic arterial pressure; GCS, Glasgow coma scale; WBC, white blood cell; Hb, haemoglobin.\* The preoperative angiographic stages are evaluated according to the classification described by Suzuki and Takaku<sup>11</sup>

	Cerebral hyperperfusion (n=47)	No cerebral hyperperfusion (n=52)	P-value
Age [yr, mean (range)]	39 (19–61)	40 (19–58)	0.772
Sex (M:F)	14:33	11:41	0.361
Initial presentation (haemorrhage:infarction:TIA)	2:19:26	4:28:20	0.231
Angiographic staging* (III:IV)	40:7	43:9	0.791
Significant decreased perfusion on SPECT (n)	21	20	0.672
HSAP (mm Hg)	139 (16)	137 (15)	0.563
LSAP (mm Hg)	113 (10)	114 (12)	0.694
HDAP (mm Hg)	88 (11)	87 (11)	0.893
LDAP (mm Hg)	69 (10)	69 (10)	0.969
GCS at admission	15 (0)	15 (0)	1.000
Preoperative WBC ( $10^3 \mu\text{l}^{-1}$ )	6.6 (1.6)	6.3 (2.0)	0.455
Preoperative Hb (g $\text{dl}^{-1}$ )	13.5 (1.4)	13.0 (1.6)	0.114

## Results

Among 82 consecutive patients with 99 surgeries, three patients had postoperative cerebral infarction with a new and small lesion on neuroimaging. But, their neurological deficits were transient and improved at hospital discharge. Two patients had re-operation in the immediate postoperative period due to epidural haematoma. The patency of STA-MCA bypass was confirmed in all patients by conventional angiography, magnetic resonance angiography, or both.

Thirty-nine patients (47 sides, 47%) suffered from SCH from 1 to 9 days after surgery (median: 2 days), which was sustained for 1 to 14 days (median: 7 days). The main presentations corresponded to dysfunctions around the bypass site at the perisylvian area, including dysarthria, hand motor dysfunction, and motor or sensory dysphasia. Seizure was shown in four patients. Only two patients showed symptomatic subarachnoid haemorrhage. All patients with SCH showed a significant focal increase in cerebral blood flow at the site of the anastomosis on

postoperative SPECT, whereas postoperative MRI/MRA or CT showed no ischaemic changes.

There was no significant difference in preoperative factors between patients with SCH and those without (Table 1). Significant differences were demonstrated in the operation of the dominant hemisphere ( $P<0.001$ ) and WBC count on postoperative day 0, day 1, and day 2 ( $P=0.049$ , 0.013, 0.019 each, Tables 2 and 3). On binary logistic regression, the operative side of the dominant hemisphere was a significant independent factor for SCH (Table 4). WBC count on postoperative day 1 was also significantly correlated with SCH.

There was no significant difference in hospital mortality between two groups. Patients with SCH had longer hospital and ICU stays than those without ( $P<0.01$ , Table 5).

## Discussion

This study showed that the incidence of cerebral hyperperfusion after STA-MCA anastomosis was high in adult patients with moyamoya disease, and that the operative side of the

**Table 2** Intraoperative factors. Data are presented as numbers or mean (sd). HSAP and LSAP, the highest and lowest systolic arterial pressure; HDAP and LDAP, the highest and lowest diastolic arterial pressure,  $HPa_{CO_2}$  and  $LPa_{CO_2}$ , the highest and lowest arterial carbon dioxide tension; LHct, the lowest haematocrit. \*Data were collected in 27 patients (14 in the cerebral hyperperfusion group, 13 in the no cerebral hyperperfusion group)

	Cerebral hyperperfusion (n=47)	No cerebral hyperperfusion (n=52)	P-value
Surgical time (min)	381 (72)	353 (53)	0.302
Temporal occlusion time* (min)	48 (24)	40 (11)	0.316
Propofol–remifentanyl:sevoflurane–remifentanyl	37:10	40:12	1.000
The operation on dominant hemisphere	36	20	<0.001
Fluid balance during surgery (ml)	1509 (1132)	1242 (1123)	0.242
HSAP (mm Hg)	167 (22)	169 (22)	0.706
LSAP (mm Hg)	96 (10)	95 (11)	0.525
HDAP (mm Hg)	91 (13)	90 (15)	0.861
LDAP (mm Hg)	46 (7)	45 (7)	0.476
Arterial pressure			0.302
Hypotension (n)	0	0	
Normotension (n)	41	49	
Hypertension (n)	6	3	
$HPa_{CO_2}$ (kPa)	5.7 (0.5)	5.6 (0.4)	0.169
$LPa_{CO_2}$ (kPa)	4.8 (0.4)	4.8 (0.4)	0.866
$Pa_{CO_2}$ (kPa)			0.414
<4.7	12	14	
4.7–6.0	25	32	
>6.0	10	6	
LHct (%)	29 (4)	29 (4)	0.909
Intraoperative transfusion (n)	30	34	1.000

**Table 3** Postoperative factors. Data are presented as mean (sd). APACHE, Acute Physiology and Chronic health Evaluation; SAP and DAP, immediate postoperative systolic and diastolic arterial pressure; Hb POD0 and Hb POD1, immediate postoperative and the first postoperative day haemoglobin; WBC POD0, immediate postoperative white blood cell; WBC POD1 and WBC POD4, the first and fourth postoperative white blood cell. \*Data were collected in 62 patients (28 in the cerebral hyperperfusion group, 34 in the no cerebral hyperperfusion group)

	Cerebral hyperperfusion (n=47)	No cerebral hyperperfusion (n=52)	P-value
APACHE II score	8.1 (8.0)	7.1 (6.3)	0.499
SAP (mm Hg)	144 (23)	145 (25)	0.380
DAP (mm Hg)	81 (14)	85 (14)	0.158
Hb POD0 (g dl <sup>-1</sup> )	12.4 (1.2)	12.5 (1.2)	0.774
Hb POD1 (g dl <sup>-1</sup> )	12.2 (1.2)	12.4 (1.1)	0.414
WBC POD0 (10 <sup>3</sup> μl <sup>-1</sup> )	11.3 (3.5)	10.0 (2.9)	<b>0.049</b>
WBC POD1 (10 <sup>3</sup> μl <sup>-1</sup> )	12.0 (3.3)	10.4 (2.7)	<b>0.013</b>
WBC POD4 (10 <sup>3</sup> μl <sup>-1</sup> )*	8.4 (3.4)	6.5 (2.1)	<b>0.019</b>

dominant hemisphere and postoperative increased WBC count were significantly correlated with SCH.

Cerebral hyperperfusion syndrome after extracranial–intracranial bypass results from a rapid increase in cerebral blood flow in the chronic ischaemic brain. Two previous reports demonstrated that the incidence of temporary neurological deterioration due to hyperperfusion after STA-MCA anastomosis was as high as about 40% in patients with adult-onset moyamoya disease.<sup>5 12</sup> In this study, the incidence of symptomatic hyperperfusion (47%) was likely to

be higher than that shown in previous reports. We think that the possibility of a false positive is very low because the occurrence of SCH was double-checked by a neurosurgeon and our criteria for SCH were already used in many previous studies concerning cerebral hyperperfusion after revascularization in moyamoya patients.<sup>5–8 10 13 14</sup> Our results both confirm and expand the findings of previous reports that STA-MCA anastomosis for moyamoya disease, which usually provides low-flow revascularization because of the relatively small diameter of the recipient artery, can



**Table 4** Independent predictors for SCH after STA-MCA anastomosis in adult patients with moyamoya disease on binary logistic regression. WBC POD1, the first postoperative white blood cell. \*Adjusted for initial symptoms, preoperative haemoglobin, fluid balance during surgery, intraoperative the highest arterial carbon dioxide tension, and diastolic arterial pressure just after admission to ICU, which are factors with a *P*-value of <0.25 in Tables 1–3. Nagelkerke *R*<sup>2</sup> statistic was 0.247. The Hosmer and Lemeshow goodness of fit test was not significant at 5% (*P*=0.671)

	Symptomatic cerebral hyperperfusion*		
	Risk ratio	95% confidence interval	<i>P</i> -value
The operation on dominant hemisphere	5.09	2.07–12.54	<0.001
WBC POD1 (10 <sup>3</sup> μl <sup>-1</sup> )	1.19	1.02–1.38	0.029

**Table 5** The comparison of hospital course in both patients with symptomatic cerebral hyperperfusion after STA-MCA anastomosis and those without in adult patients with moyamoya disease. Data are presented as numbers or mean (sd)

	Cerebral hyperperfusion (n=47)	No cerebral hyperperfusion (n=52)	<i>P</i> -value
Hospital mortality	0	0	1.000
ICU length of stay (days)	5.0 (2.5)	3.7 (1.0)	0.001
Hospital stay (days)	15 (5)	12 (3)	0.001

result in SCH.<sup>5–8 10 13 14</sup> Fujimura and colleagues<sup>15</sup> also reported that SCH was a potential complication of STA-MCA anastomosis, especially in patients with moyamoya disease.

It is clinically important to identify predictors for SCH after STA-MCA anastomosis in patients with moyamoya disease. Risk factors for cerebral hyperperfusion after carotid endarterectomy are well documented,<sup>16</sup> whereas those for SCH after STA-MCA anastomosis in moyamoya disease are not fully investigated. Of interest, this study showed that high postoperative WBC count was associated with postoperative SCH. In this study, no patient showed an evidence of overt infection until at least the fourth postoperative day. Therefore, such finding suggests that inflammation may play a role in developing cerebral hyperperfusion injury after direct revascularization in patients with moyamoya disease. It is well known that inflammation is involved in the pathogenesis of some vascular diseases such as coronary artery disease, atherosclerosis, and vasospasm after aneurysmal subarachnoid haemorrhage.<sup>17–19</sup> Also, the increased expression of serum inflammatory molecules in patients with moyamoya disease was reported previously.<sup>20</sup> The up-regulation of interleukin-1β may be associated with greater vasodilation

and pial hyperaemia developed after direct revascularization in patients with moyamoya disease. Elevated levels of interleukin-1 result in macrophage activation, increased vascular permeability, and endothelial dysfunction.<sup>21</sup> A previous *in vitro* study showed that interleukin-1β significantly increased the release of prostaglandin E2, a potent vasodilator, in arterial smooth muscle cells derived from patients with moyamoya disease.<sup>22</sup> The expression of vascular endothelial growth factor and matrix metalloproteinase-9, which have a potential role to increase the permeability of the blood–brain barrier, is significantly increased in moyamoya patients compared with healthy control subjects.<sup>23 24</sup> Oxygen-derived free radicals as a possible mediator of impaired autoregulation can cause damage to the cerebrovascular endothelium, resulting in postoperative hyperperfusion.<sup>25 26</sup> Taken together, we speculate that an inflammatory process leading to cerebral hyperperfusion may occur before symptoms are fully manifested, and a raised postoperative WBC count is likely to be a marker of the inflammatory process, which may be involved in the pathogenesis of SCH. But, because we did not measure other inflammatory molecules associated with cerebral hyperperfusion, except WBC count, in this study, we had a limitation in showing a causality of inflammation for producing cerebral hyperperfusion. A further prospective study should be needed to verify the relationship of inflammation and postoperative cerebral hyperperfusion in moyamoya disease.

In this study, the site of anastomosis, especially on the dominant hemisphere, was a predictable factor for postoperative SCH. Indeed, our result showed that the symptoms of postoperative transient neurological deterioration correlated well with cortical dysfunctions around the left perisylvian area, most frequently including hand and tongue motor dysfunction and dysphasia. Such finding was supported by a previous study, in which clinical symptoms of temporary neurological deterioration were completely associated with transient relative hyperperfusion around the recipient artery, and the incidence of temporal hyperperfusion was higher in the functionally relevant hemisphere.<sup>10</sup>

A previous study indicated that patients' age and the type of the onset were the significant factors to predict postoperative symptomatic hyperperfusion in patients with moyamoya disease.<sup>6</sup> In contrast to the report, this study showed that patients' age and the type of the onset were not associated with postoperative symptomatic hyperperfusion. The main reason is due to the difference in the study population. In this study, only adult patients were enrolled, whereas paediatric patients and adults participated in that study. In addition, the portion of haemorrhagic-onset patients was much lower than that of those with infarction or transient ischaemic attack in our study. So, we did not evaluate the effects of age and the type of the onset on postoperative symptomatic hyperperfusion in this study.

A possibility that a tiny focal cerebral ischaemic insult, which is invisible in postoperative imaging studies, may be deemed as SCH is considered. Such a situation may occur because of temporary occlusion of the recipient artery

during anastomosis, sacrifice of small penetrating branches of the recipient artery, and arterial pressure fluctuation during surgery. However, we cannot be certain of the contribution of these factors to symptomatic hyperperfusion, because neurological deterioration occurred on the second postoperative day in most patients with SCH.

The major interest during the postoperative period is arterial pressure control in moyamoya patients who underwent STA-MCA bypass. Lowering arterial pressure in patients with SCH is an effective treatment after direct revascularization surgery for moyamoya disease.<sup>6, 15</sup> A recent study reported the importance of prophylactic arterial pressure decrease in preventing SCH after STA-MCA anastomosis in patients with moyamoya disease.<sup>27</sup> But, aggressive arterial pressure lowering in all patients should be cautious because of the risk of perioperative ischaemic complications.<sup>28</sup> Although arterial pressure during the intra- and postoperative period was strictly controlled in this study, we think that arterial pressure should be more actively managed in patients with dominant side operations because the operation on the dominant side was an important risk factor of SCH.

This study had some limitation. This study was retrospectively conducted in a single centre. In addition, the small sample may affect the ability to detect significant findings in some instances. C-reactive protein, a sensitive marker of inflammation, was not measured in this study. A variety of inflammatory markers related to neutrophil chemotaxis and diapedesis and also C-reactive protein should be investigated in a further study to verify an association of inflammation and SCH. Also, although we have found an association between a raised postoperative WBC count and SCH, we recommend caution in interpreting this finding since the association was weak (Nagelkerke  $R^2$  statistic was 0.247) and causality was not evident.

In conclusion, the operation on the dominant hemisphere and increased postoperative WBC count were associated with postoperative transient neurological deterioration due to cerebral hyperperfusion after STA-MCA anastomosis in adult patients with moyamoya disease.

## Declaration of interest

None declared.

## Funding

None.

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