ORIGINAL PAPER

Satoshi Kuroda
Kiyohiro Houkin
Tatsuya Ishikawa
Naoki Nakayama
Jun Ikeda
Nobuaki Ishii
Hiroyasu Kamiyama
Yoshinobu Iwasaki

Determinants of intellectual outcome after surgical revascularization in pediatric moyamoya disease: a multivariate analysis

S. Kuroda (✉) · K. Houkin · T. Ishikawa ·
N. Nakayama · J. Ikeda · N. Ishii ·
H. Kamiyama · Y. Iwasaki
Department of Neurosurgery,
Hokkaido University Graduate
School of Medicine,
North 15 West 7, Kita-ku, Sapporo
060-8638, Japan
e-mail: skuroda@med.hokudai.ac.jp
Tel.: +81-11-716-1161
Fax: +81-11-708-7737

Abstract *Objects:* The aim of this study was to clarify predictors for poor intellectual outcome in pediatric moyamoya disease. *Methods:* Fifty-two pediatric patients were included. Clinical diagnosis was transient ischemic attacks (TIA) in 35 and completed stroke in 17. Ten patients underwent indirect synangiosis through "small craniotomy," whereas the other 42 underwent superficial temporal artery (STA)–middle cerebral artery (MCA) anastomosis and indirect synangiosis through "large craniotomy." Full-scale IQ (FSIQ) was measured using the Wechsler intelligence scale for children (WISC) after surgery. Multivariate logistic regression models were applied to test the effect of clinical factors on intellectual outcome. *Results and conclusion:* Eight patients revealed mentally impaired status (FSIQ<70). Multivariate analysis revealed that completed stroke and "small craniotomy" surgery were significantly associated with poor intellectual outcome. Odds ratios of each factor were 33.4 (95% CI, 2.4–474) and 19.6 (95% CI, 1.8–215) respectively. Early diagnosis and the revascularization procedure over as wide an area as possible may be essential to improve their intellectual outcome.

Keywords Moyamoya disease · Intellectual outcome · Surgical revascularization · Ischemia · Cerebral blood flow

Introduction

Moyamoya disease is characterized by stenosis or occlusion of the terminal portion of the internal carotid artery (ICA) bilaterally. Furthermore, an abnormal net-like vascular network can be seen in the region of the basal ganglia and thalamus, known as "moyamoya" vessels [23]. The incidence of moyamoya disease has been particularly high among far-east Asian countries including Japan and Korea. The underlying pathogenesis is still obscure [2]. Moyamoya disease occurs in both children and adults. Most pediatric patients develop transient ischemic attacks (TIA) or cerebral infarction due to critical blood flow reduction in the ICA territory. Previous reports have clarified that surgical revascularization including superficial temporal artery (STA)–middle cerebral artery (MCA) anastomosis and indirect synangiosis

can improve cerebral hemodynamics [7, 14, 25], and resolve ischemic attacks in them [10, 12, 20]. With regard to stroke recurrence and activities of daily living (ADLs), postoperative long-term outcome is favorable.

However, it is also known that intellectual development is impaired in a certain subgroup of pediatric patients [3, 16]. Even after surgical revascularization, intellectual impairment has been reported to disturb an independent social life in more than 20% of the patients [8, 10, 17, 20]. Some studies have suggested that cerebral infarction may be related to poor intellectual outcome. Surgical procedures may have some effect on intellectual outcome [10]. However, there are few reports that defined statistically significant predictors of poor intellectual outcome in pediatric patients with moyamoya disease.

Therefore, in the present study, we aimed to clarify significant predictors of poor intellectual outcome during

follow-up periods after surgical revascularization. For this purpose, a multivariate analysis was performed to adjust various confounding factors.

Materials and methods

Study design, patients, and surgical treatment

Fifty-two pediatric patients who presented TIA and/or ischemic stroke due to moyamoya disease between 1980 and 2000 underwent surgical revascularization at Hokkaido University Hospital. All patients were diagnosed with moyamoya disease by cerebral angiography. There were 21 boys and 31 girls. They experienced their first ischemic episode between 1 and 14 years of age (mean ± SD: 5.7±3.3 years). Clinical diagnosis was TIA in 35 patients and completed stroke (CS) in 17. Plain CT scan and/or MRI were performed to define the location of the cerebral infarction. Twenty-nine patients had no cerebral infarction. Another 12 patients had a small infarction in the deep white matter, and the remaining 11 had a large infarction in the cerebral cortex. None of the patients had any cardiovascular, pulmonary, and renal complications. Mean preoperative diseased period between the onset and surgery was 2.7±2.9 years.

Surgical revascularization was performed on both hemispheres in 47 out of 52 patients. The other 5 patients underwent it on only one side because the contralateral hemisphere had only a mild occlusive change in the carotid fork and normal hemodynamics on single photon emission computed tomography (SPECT) [13, 14]. During the first 6 years, 10 patients underwent indirect bypass surgery (encephalo-myo-synangiosis [EMS] or encephalo-myo-arterio-synangiosis [EMAS]) through a small craniotomy over the temporo-parietal areas. Briefly, a horseshoe-shaped skin incision was made surrounding the parietal branch of the STA. The parietal branch of the STA was preserved patent, and the temporal muscle was dissected all along the horseshoe incision. Then, a craniotomy was performed followed by the opening of the dura mater. The dura was removed along the middle meningeal artery, which was left intact. The parietal branch of the STA and temporal muscle were placed over the brain surface, and the temporal muscle was sutured to the dural edge ("small craniotomy" group; Fig. 1). Subsequently, 42 patients underwent combined bypass surgery, including STA–MCA anastomosis and encephalo-duro-arterio-myo-synangiosis (EDAMS) [5]. Briefly, a skin incision was made from the temporal to the frontal area. The parietal and frontal branches of the STA were carefully dissected under the microscope. The temporal muscle was separated as widely as possible. A fronto-temporal craniotomy was also made as widely as possible. These procedures were aimed at exposing as much of the brain surface as possible, so that indirect revascularization could be obtained as widely as possible, especially in the frontal area. The middle meningeal artery was left intact during the craniotomy and dural opening. Then, one or two branches of the STA were anastomosed to the cortical branches of the MCA under a surgical microscope, using 10–0 monofilament nylon. The temporal muscle was placed over the brain surface, and was sutured to the dural edge ("large craniotomy" group; Fig. 1).

Follow-up

All patients were followed up at an outpatient clinic. Mean follow-up period was 9.7 years ranging from 1 to 20 years. Full-scale IQ (FSIQ) was measured by using the Wechsler intelligence scale for children (WISC)-revised (R) or WISC-third edition (III) 1–4 years after surgery in all 52 patients, when they were 5 years of age and older.

Fig. 1 Photograph of skin incision (*left*) and the extent of craniotomy (*right*) of "small craniotomy" (*top*) and "large craniotomy" surgery (*bottom*)
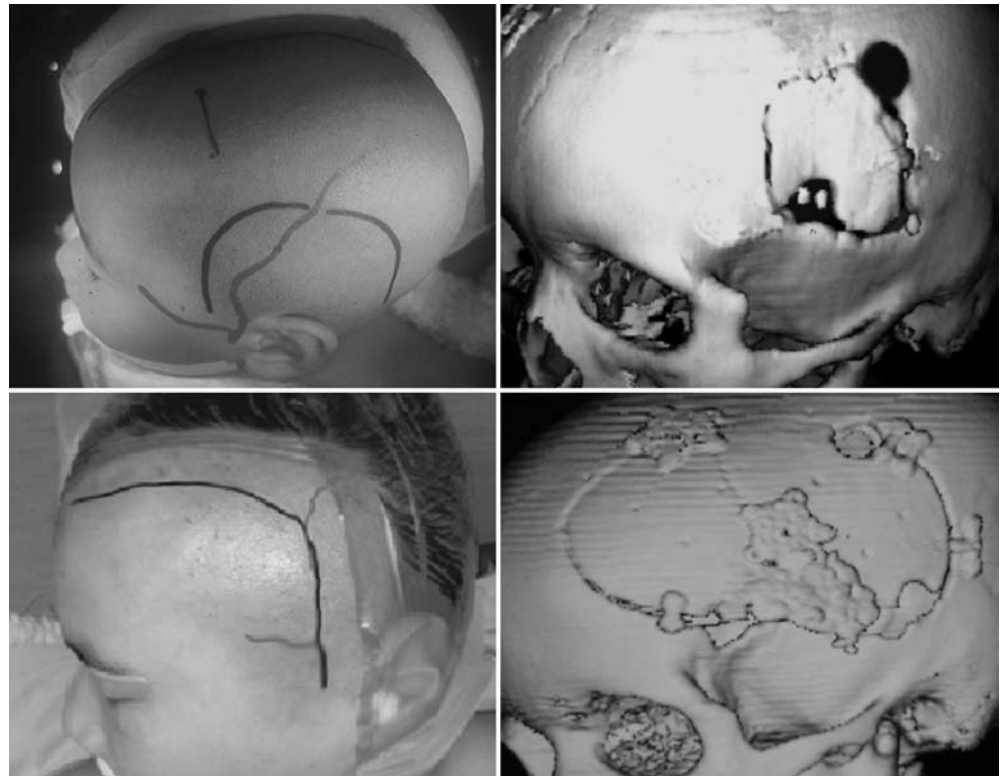
Cerebral blood flow study

Regional cerebral blood flow (rCBF) was measured to assess the effects of surgical revascularization on cerebral hemodynamics in the frontal lobe. The interval between FSIQ assessment and SPECT study ranged between 1 and 6 months. Using the ^{133}Xe inhalation method and SPECT (HEADTOME SET-031, Shimadzu Co., Kyoto, Japan), we quantitatively measured rCBF before and 15 min after injection of 10 mg/kg IV acetazolamide (acetazolamide test) [15]. rCBF was calculated by the sequential picture method described by Kanno and Lassen (cited in [15]). All regions of interest were those in which no infarction was seen on CT and MRI. Regional cerebrovascular reactivity (rCVR) to acetazolamide was quantitatively calculated as follows: $\mathrm{rCVR}(\%) = 100 \times (\mathrm{rCBF_{ACZ}} - \mathrm{rCBF_{rest}})/\mathrm{rCBF_{rest}}$, where $\mathrm{rCBF_{rest}}$ and $\mathrm{rCBF_{ACZ}}$ represent rCBF before and after intravenous injection of acetazolamide respectively.

Absolute values of rCBF are known to change strikingly with growth, and it is difficult to compare the absolute values of rCBF among children of various ages [13, 21]. In the current study, therefore, rCBF in the frontal lobe was expressed as the ratio to mean hemispheric cerebral blood flow (rCBF/mCBF) [13, 21]. As reported previously [13], control values of rCBF were obtained from 21 children free of cerebrovascular disease who were aged between 1 and 15 years (mean 11.6 years).

Statistical analysis

Primary comparisons were performed between the patients with and without poor intellectual outcome. Data were expressed as percentages or as mean ± SD. Categorical variables were compared by using a χ^2-test. Continuous variables were compared by using a two-tailed unpaired Student t-test. Differences were considered to be statistically significant if the p-value was <0.05.

A multivariate logistic regression model was conducted to test the effect on intellectual outcome of patient gender, onset age, preoperative diseased period, cerebral infarction, disease type, and procedure of bypass surgery. A forward stepwise model-building procedure was performed for the parameters, using $p<0.10$ achieved in univariate analysis. In the final multivariate analysis, the statistical level of significance was set at $p<0.05$. Statistical analysis was completed with SPSS for Windows, version 8.0 (SPSS, Inc., Chicago, USA).

Table 1 Total IQ on WISC-R or WISC-III during postoperative follow-up periods in pediatric moyamoya disease ($n=52$)

Total IQ	Meaning	n	%	% (control)
>130	Very superior	1	1.9	2.2
120–129	Superior	2	3.8	6.7
110–119	High average	5	9.6	16.1
90–109	Average	24	46.2	50.0
80–89	Low average	7	13.5	16.1
70–79	Borderline	5	9.6	6.7
Up to 69	Mentally impaired	8	15.4	2.2

Results

Full-scale IQ at follow-up

Table 1 summarizes the results of FSIQ at follow-up. FSIQ varied from 59 to 135. Intellectual examination verified 1 patient (1.9%) as very superior, 2 (3.8%) as superior, 5 (9.6%) as high average, 24 (46.2%) as average, 7 (13.5%) as low average, 5 (9.6%) as borderline, and 8 (15.4%) as mentally impaired. When compared with the distribution in normal controls in Japan [27], the incidence of the patients who were verified as mentally impaired was significantly higher than that in normal controls (15.4 and 2% respectively). There were no significant differences in the incidence of the other ranks (Table 1). In this study, therefore, intellectual outcome was decided as being "poor" when postoperative FSIQ was less than 70.

Independent predictors of poor intellectual outcome

The effects of various factors on poor intellectual outcome are shown in Table 2. There was no significant difference in poor intellectual outcome between genders ($p=0.166$, χ^2-test). Onset age was not a significant pre-

Table 2 Independent predictors of poor intellectual outcome among 52 children with moyamoya disease. *OR* odds ratio, *95% CI* 95% confidence interval, *TIA* transient ischemic attacks, *CS* completed stroke. Continuous data are expressed as mean ± SD

	Intellectual outcome		Univariate analysis	Multivariate analysis	OR (95% CI)
	Good	Poor			
Gender					
Boys	16	5	$p=0.166$		
Girls	28	3			
Onset age (years)	5.6±3.3	4.5±1.7	$p=0.368$		
Preoperative diseased period (years)	2.2±1.7	5.7±5.6	$p=0.001$	$p=0.2804$	
Cerebral infarction					
No	29	0	$p<0.0001$	$p=0.1272$	
White matter	11	1			
Cortex	4	7			
Clinical diagnosis					
TIA	34	1	$p<0.0001$	$p=0.0003$	33.4 (2.4–474)
CS	10	7			
Bypass surgery					
Small craniotomy	5	5	$p=0.001$	$p=0.0046$	19.6 (1.8–215)
Large craniotomy	39	3			

Table 3 Postoperative cerebral hemodynamics in the frontal lobe in pediatric moyamoya disease. Data are expressed as mean ± SD

	Right side		Left side	
	rCBF/mCBF	rCVR (%)	rCBF/mCBF	rCVR (%)
"Small craniotomy" group	0.97±0.06	12.6±8.0	0.92±0.05	14.0±14.7
"Large craniotomy" group	1.12±0.07	20.8±9.2	1.14±0.08	21.6±7.1
p-value	<0.0001	0.0328	<0.0001	0.0458

dictor of poor intellectual outcome (*p*=0.368, unpaired *t*-test). However, preoperative diseased period was significantly longer in poor outcome group than in good outcome group, 5.7±5.6 and 2.2±1.7 years, respectively (*p*=0.0001, unpaired *t*-test). Intellectual outcome was good in all 29 patients who had no cerebral infarction. Of 12 patients who had cerebral infarction in the deep white matter, 11 (91%) were classified into the good outcome group. On the other hand, intellectual outcome was poor in 7 (67%) of 11 patients who had cortical infarct. According to the results, cerebral infarction was associated with poor intellectual outcome (*p*<0.0001, χ^2-test). Likewise, completed stroke and "small craniotomy" surgery were also significantly related to poor intellectual outcome (*p*<0.00001 and *p*=0.001 respectively, χ^2-test). These four factors, therefore, were included in the logistic regression analysis. As shown in Table 2, the model indicated two independent factors as predictors of poor intellectual outcome: completed stroke (odds ratio (OR), 33.4; 95% confidence interval (CI), 2.4–474; *p*=0.0003) and "small craniotomy" surgery (OR, 19.6; 95% CI, 1.8–215; *p*=0.0046). In this model, correct classification was obtained in 94.2% of the cases.

Cerebral hemodynamics in the frontal lobe

The rCBF/mCBF ratio and rCVR to acetazolamide were analyzed to elucidate whether surgical procedures have an effect on cerebral hemodynamics in the frontal lobe, because multivariate analysis revealed that "small craniotomy" surgery confined to the temporo-parietal region could be an significant predictor of poor intellectual outcome. Postoperative SPECT measurements were performed in 9 patients who underwent "small craniotomy" surgery and in 38 patients who underwent "large craniotomy" surgery.

Table 3 summarizes the results of postoperative SPECT studies. Thus, rCBF/mCBF ratios in the right and left frontal lobe were 0.966±0.059 and 0.923±0.045 respectively after "small craniotomy" surgery. However, rCBF/mCBF ratios in the right and left frontal lobe were 1.116±0.066 and 1.137±0.076 respectively after "large craniotomy" surgery. There were statistically significant differences between surgical procedures on both sides (*p*<0.0001, unpaired *t*-test). In the patients who underwent "small craniotomy" surgery, postoperative rCBF/mCBF ratios in the bilateral frontal lobes were significantly
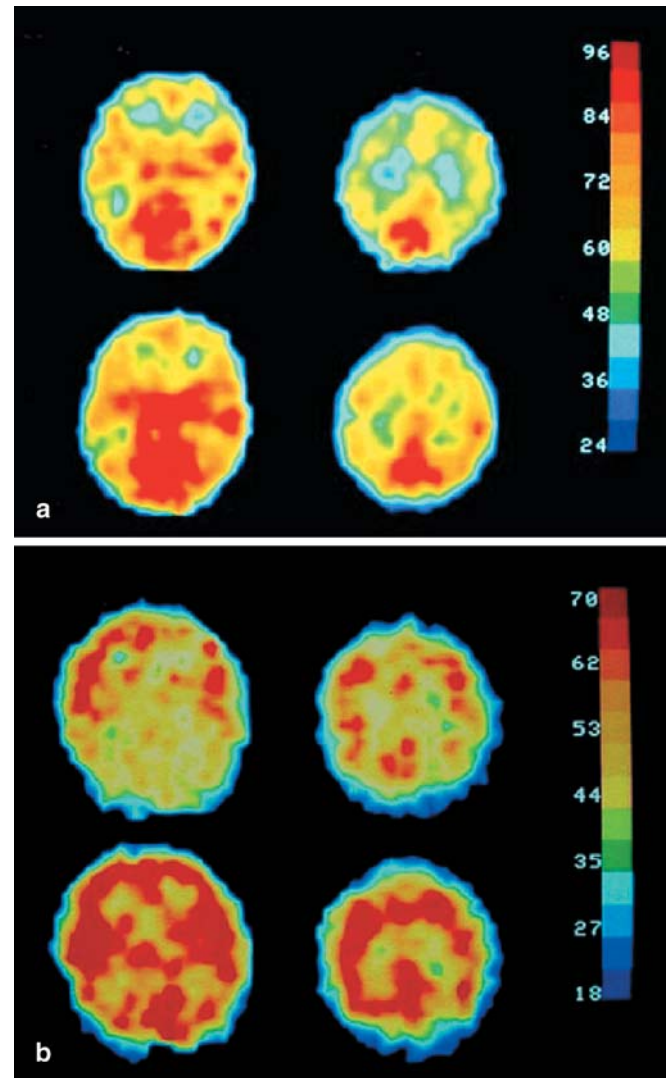

Fig. 2 Representative single photon emission tomography after **a** "small craniotomy" or **b** "large craniotomy" surgery. Cerebral blood flow was measured before (*top*) and after intravenous injection of 10 mg/kg acetazolamide (*bottom*)

lower than that obtained from control children (1.140±0.050, *p*<0.0001).

On the other hand, rCVR to acetazolamide in the right and left frontal lobe was 12.6±8.0 and 14.0±14.7% after "small craniotomy" surgery. After "large craniotomy" surgery, the values were 20.8±9.2 and 21.6±7.1% re-

spectively. Unpaired *t*-test revealed significant differences between surgical procedures on both sides (*p*=0.0328 on the right side, *p*=0.0458 on the left side). Representative SPECT data after each surgery are shown in Fig. 2.

Discussion

Intellectual outcome in moyamoya disease

Based on previous reports, the natural course of intellectual outcome is poor in pediatric patients with moyamoya disease. More than one-third of them were poorly educable [3, 16]. Kurokawa et al. evaluated the natural course of pediatric patients with moyamoya disease, and reported that mild intellectual and/or motor impairment was observed in 26% of them, special school or care by parents/institution in teenage years in 11%, and total 24-h care in 7% [16]. According to these studies, poor intellectual outcome was correlated with early onset, completed stroke, or a longer diseased period [3, 16].

Although surgical revascularization is known to resolve TIA and ischemic stroke very effectively, intellectual delay is still a serious problem for a certain subgroup of pediatric patients and their families even after surgery. Previous studies have clarified that about 10–30% of the patients had difficulty in social or school life because of intellectual impairment [10, 12, 17, 19, 20]. These reports have suggested that completed stroke, cerebral infarction, and early onset (<5 years) may have significant effects on intellectual outcome. It has also been suggested that the procedures of surgical revascularization may have some influence on intellectual outcome [10]. Previously, however, significant predictors of poor intellectual outcome after surgery have not been fully analyzed. Using a univariate analysis model, Matsushima et al. reported that there was no significant factor for intellectual outcome after encephalo-duro-arterio-synangiosis (EDAS) [19]. However, their study had some bias in the patient selection, because they excluded the patients with FSIQ below 70, and they did not perform a multivariate analysis probably because of the small sample size (*n*=20) [19].

Determinants of intellectual outcome

In the current study, therefore, the authors assessed significant factors for poor intellectual outcome in the pediatric patients who underwent surgical revascularization, in order to make therapeutic strategies better and improve their intellectual outcome. Based on the data from a multivariate analysis, the present study revealed that completed stroke (CS) and "small craniotomy" surgery were independent predictors of poor intellectual outcome in pediatric patients with moyamoya disease (Table 2).

Contrary to previous reports, age at onset, preoperative diseased period, and cerebral infarction were not significant factors. Most of the CS-type patients already had hemiparesis or tetraparesis before surgical revascularization, indicating that poor intellectual outcome is closely related to the impairment of motor function. Previous studies have clarified that the incidence of CS-type patients is extremely high in a subgroup of patients who develop ischemic attacks in very early childhood (<2 years) or who did not undergo surgical treatment for a long time [2, 8, 10, 16]. The present result, therefore, strongly suggests that diagnosis and surgical intervention as early as possible would possibly reduce the incidence of completed stroke and may improve their intellectual outcome even in these patients. For this purpose, MRI and MRA can be a non-invasive and powerful modality for diagnosing moyamoya disease in its early stage [4]. There is increasing evidence that T1-weighted images can detect the dilated moyamoya vessels in the basal ganglia and periventricular white matter, and that MRA can directly visualize the occlusive lesion in the carotid forks and moyamoya vessels with high specificity and sensitivity. In particular, a screening test for children at high risk, i.e., those who have a moyamoya patient among their blood relatives, is clinically important, because familial occurrence is reported in more than 10% of patients [4].

Another independent predictor of poor intellectual outcome was "small craniotomy" surgery. There were no reports that clearly defined the effect of surgical procedures on intellectual outcome. Indirect procedures such as EDAS and EMS are very easy, and have been widely performed in patients with moyamoya disease [2]. However, one of the disadvantages is the fact that the revascularized area is limited and is confined to the craniotomy field after these procedures [18, 22, 24]. Previous reports have pointed out that, regardless of the disappearance of ischemic attacks, intellectual outcome was poor in a majority of the patients who underwent these procedures [22]. Thus, Sato et al. reported that intellectual outcome was poor in 9 out of 13 children who underwent EMS/EDAS, although none of them suffered recurrent ischemic attacks [22].

It is not fully understood why "small craniotomy" was proved to be an independent predictor of poor intellectual outcome. As described above, we performed indirect bypass surgery through a "small craniotomy" over the temporo-parietal region during the first 6 years. Subsequently, however, we shifted to perform STA–MCA anastomosis and indirect bypass surgery through a "large craniotomy" over the frontal, temporal, and parietal regions (Fig. 1). STA–MCA anastomosis has the benefit of directly supplying collateral blood flow to the ischemic brain immediately after surgery. In fact, the incidence of perioperative ischemic stroke was lower in the patients who underwent STA–MCA anastomosis and EDAMS than in those who only underwent indirect synangiosis

[10]. About 3 months after surgery, however, neovascularization through indirect synangiosis developed very well in the pediatric patients, playing a major role as the collateral circulation thereafter [6]. Therefore, STA–MCA anastomosis itself is not an important factor for intellectual outcome during a long-term follow-up. A wide-ranging craniotomy and indirect synangiosis extending to the frontal region may play a crucial role in improving their intellectual outcome.

Frontal lobe and intellectual outcome

Based on the current results, chronic blood flow reduction in the frontal lobe may be responsible for poor intellectual outcome, because "small craniotomy" surgery cannot supply collateral blood flow to the area beyond the surgical field, especially to the frontal area. Thus, the extent of the collateral formation depends on the size of craniotomy and dural opening [18, 24]. Several studies have shown that revascularization surgery through a "small craniotomy" does not improve cerebral hemodynamics in the frontal lobe [11, 18, 22, 24]. Using SPECT, Sato et al. showed that blood flow improved in a limited area around the surgical field, and that blood flow reduction is persistent in the frontal lobe even after EDAS/EMS [22]. Isobe et al. also measured blood flow and cerebrovascular reactivity after bypass surgery, and showed that cerebral hemodynamics was markedly impaired in the frontal lobe in the patients who underwent indirect synangiosis through a "small craniotomy" [11]. On the other hand, STA–MCA anastomosis and EDAMS through a "large craniotomy" could normalize rCBF distribution and cerebrovascular reactivity to acetazolamide in the frontal lobe [11, 14]. Using cerebral angiography, furthermore, Takahashi et al. reported that collateral development was confined to the parietal region in the patients who underwent "small craniotomy" surgery, whereas extensive collaterals were developed in the frontal, temporal, and parietal lobes in those who underwent "large craniotomy" surgery [24].

Although the relationship between intellectual development and frontal lobe function in children still remains obscure, recent studies have suggested a close correlation between them [1]. Based on these considerations, it is strongly recommended that indirect synangiosis should be performed over as wide an area as possible using all of the available tissue that has revascularizing potential, especially over the frontal lobe, in order to improve their intellectual outcome.

Limitation of the current study

Little is known about longitudinal changes of intellectual development in pediatric patients with moyamoya disease before and after surgical revascularization. Imaizumi et al. (1999) reported that their IQ gradually decreases over long periods of more than 10 years, when they were treated conservatively [9]. However, there is no report that clearly defines whether or not surgical revascularization improves or maintains their intellectual status. In fact, the present study could not elucidate this because intellectual status was evaluated before surgery in only about half of the patients. Prospective investigations will be necessary to clarify the question.

The prospective randomized clinical trial (RCT) with low likelihoods of false-positive and false-negative errors has been accepted to provide the highest level of evidence (level I) that can be applied to a clinical recommendation. However, no RCT has been performed to analyze therapeutic effects in pediatric patients with moyamoya disease, probably because of the small number of patients (the annual incidence, 0.35 per 100,000 population) [26]. In the present study, all patients who were diagnosed with moyamoya disease at our hospital were included, and underwent surgical revascularization, either "small craniotomy" surgery or "large craniotomy" surgery. Surgical procedures were not randomized. All patients were followed up in an outpatient clinic, and intellectual outcome was evaluated during postoperative follow-up periods. Therefore, the present study is a non-randomized historical cohort study, and provides level IV evidence. Level IV evidence can support grade C recommendations. Grade C recommendations often present an array of potential clinical actions, any of which could be considered appropriate. Stronger evidence of therapeutic strategies to improve their intellectual outcome is expected in the future.

Conclusions

The present study revealed that completed stroke and "small craniotomy" surgery were independent predictors of poor intellectual outcome in pediatric patients with moyamoya disease. Early diagnosis and the revascularization procedure over as wide an area as possible would be essential to improve their intellectual outcome.

References

1. Filley CM (2000) Clinical neurology and executive dysfunction. Semin Speech Lang 21:95–108
2. Fukui M (1997) Current state of study on moyamoya disease in Japan. Surg Neurol 47:138–143
3. Fukuyama Y, Umezu R (1985) Clinical and cerebral angiographic evolutions of idiopathic progressive occlusive disease of the circle of Willis ("moyamoya" disease) in children. Brain Dev 7:21–37
4. Houkin K, Aoki T, Takahashi A, Abe H (1994) Diagnosis of moyamoya disease with magnetic resonance angiography. Stroke 25:2159–2164
5. Houkin K, Kamiyama H, Takahashi A, Kuroda S, Abe H (1997) Combined revascularization surgery for childhood moyamoya disease: STA–MCA and encephalo-duro-arterio-myo-synangiosis. Childs Nerv Syst 13:24–29
6. Houkin K, Kuroda S, Ishikawa T, Abe H (2000) Neovascularization (angiogenesis) after revascularization in moyamoya disease. Which technique is most useful for moyamoya disease? Acta Neurochir (Wien) 142:269–276
7. Ikezaki K, Matsushima T, Kuwabara Y, Suzuki SO, Nomura T, Fukui M (1994) Cerebral circulation and oxygen metabolism in childhood moyamoya disease: a perioperative positron emission tomography study. J Neurosurg 81:843–850
8. Imaizumi T, Hayashi K, Saito K, Osawa M, Fukuyama Y (1998) Long-term outcomes of pediatric moyamoya disease monitored to adulthood. Pediatr Neurol 18:321–325
9. Imaizumi C, Imaizumi T, Osawa M, Fukuyama Y, Takeshita M (1999) Serial intelligence test scores in pediatric moyamoya disease. Neuropediatrics 30:294–299
10. Ishikawa T, Houkin K, Kamiyama H, Abe H (1997) Effects of surgical revascularization on outcome of patients with pediatric moyamoya disease. Stroke 28:1170–1173
11. Isobe M, Kuroda S, Kamiyama H, Abe H, Mitumori K (1992) Cerebral blood flow reactivity to hyperventilation in children with spontaneous occlusion of the circle of willis (moyamoya disease). No Shinkei Geka 20:399–407
12. Karasawa J, Touho H, Ohnishi H, Miyamoto S, Kikuchi H (1992) Long-term follow-up study after extracranial–intracranial bypass surgery for anterior circulation ischemia in childhood moyamoya disease. J Neurosurg 77:84–89
13. Kuroda S, Kamiyama H, Abe H, Yamauchi T, Kohama Y, Houkin K, Mitsumori K (1993) Cerebral blood flow in children with spontaneous occlusion of the circle of Willis (moyamoya disease): comparison with healthy children and evaluation of annual changes. Neurol Med Chir (Tokyo) 33:434–438
14. Kuroda S, Houkin K, Kamiyama H, Abe H, Mitsumori K (1995) Regional cerebral hemodynamics in childhood moyamoya disease. Childs Nerv Syst 11:584–590
15. Kuroda S, Houkin K, Kamiyama H, Mitsumori K, Iwasaki Y, Abe H (2001) Long-term prognosis of medically treated patients with internal carotid or middle cerebral artery occlusion: can acetazolamide test predict it? Stroke 32:2110–2116
16. Kurokawa T, Tomita S, Ueda K, Narazaki O, Hanai T, Hasuo K, Matsushima T, Kitamura K (1985) Prognosis of occlusive disease of the circle of Willis (moyamoya disease) in children. Pediatr Neurol 1:274–277
17. Matsushima Y, Aoyagi M, Masaoka H, Suzuki R, Ohno K (1990) Mental outcome following encephaloduroarteriosynangiosis in children with moyamoya disease with the onset earlier than 5 years of age. Childs Nerv Syst 6:440–443
18. Matsushima T, Inoue T, Suzuki SO, Fujii K, Fukui M, Hasuo K (1992) Surgical treatment of moyamoya disease in pediatric patients—comparison between the results of indirect and direct revascularization procedures. Neurosurgery 31:401–405
19. Matsushima Y, Aoyagi M, Nariai T, Takada Y, Hirakawa K (1997) Long-term intelligence outcome of post-encephalo-duro-arterio-synangiosis childhood moyamoya patients. Clin Neurol Neurosurg 99 [Suppl 2]:S147–S150
20. Miyamoto S, Akiyama M, Nagata I, Karasawa J, Nozaki K, Hashimoto N, Kikuchi H (1998) Long-term outcome after STA–MCA anastomosis for moyamoya disease. Neurosurg Focus 5:1–4
21. Ogawa A, Yoshimoto T, Suzuki J, Sakurai Y (1990) Cerebral blood flow in moyamoya disease. Part 1. Correlation with age and regional distribution. Acta Neurochir (Wien) 105:30–34
22. Sato H, Sato N, Tamaki N, Matsumoto S (1990) Chronic low-perfusion state in children with moyamoya disease following revascularization. Childs Nerv Syst 6:166–171
23. Suzuki J, Takaku A (1969) Cerebrovascular "moyamoya" disease. Disease showing abnormal net-like vessels in base of brain. Arch Neurol 20:288–299
24. Takahashi A, Kamiyama H, Houkin K, Abe H (1995) Surgical treatment of childhood moyamoya disease—comparison of reconstructive surgery centered on the frontal region and the parietal region. Neurol Med Chir (Tokyo) 35:231–237
25. Touho H, Karasawa J, Ohnishi H (1996) Preoperative and postoperative evaluation of cerebral perfusion and vasodilatory capacity with 99mTc-HM-PAO SPECT and acetazolamide in childhood moyamoya disease. Stroke 27:282–289
26. Wakai K, Tamakoshi A, Ikezaki K, Fukui M, Kawamura T, Aoki R, Kojima M, Lin Y, Ohno Y (1997) Epidemiological features of moyamoya disease in Japan: findings from a nationwide survey. Clin Neurol Neurosurg 99 [Suppl 2]:S1–S5
27. Wechsler D (1998) Manual for the Wechsler intelligence scale for children, 3rd edn (Japanese version). The Psychological Corporation, San Antonio