Title: Impact of posterior cerebral artery involvement on long-term clinical and social outcome of pediatric moyamoya disease

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Impact of posterior cerebral artery involvement on long-term clinical and social outcome of pediatric moyamoya disease

Clinical article

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Object. In the study of pediatric moyamoya disease, information on long-term social outcomes and risk factors for unfavorable social outcomes remains insufficient. The authors analyzed the long-term results of surgical revascularization for pediatric patients with moyamoya disease to determine whether the involvement of a stenoocclusive lesion in the posterior cerebral artery (PCA), relatively common in pediatric moyamoya disease, represents an underlying predictor for unfavorable social outcomes.

Methods. Prospectively collected data on 61 consecutive patients with moyamoya disease who had undergone combined bypass surgery were analyzed. Neuroradiological features and other baseline clinical factors were incorporated into univariate and multivariate analyses to determine any association with an unfavorable social outcome, defined as difficulty attending regular school or obtaining regular employment.

Results. Posterior cerebral artery involvement detected by angiography on admission was noted in 22 (36.1%) of the 61 patients. Follow-up data were acquired in 56 patients (91.8%), and the mean follow-up period was 15.8 years. While transient ischemic attacks were eliminated in 52 (92.9%) of these 56 patients after surgery, and late-onset ischemic stroke was observed in only 1 patient during the follow-up period, 10 (17.9%) experienced an unfavorable social outcome. Although younger age at onset, longer duration between onset and surgery, infarction present on preoperative neuroradiological images, and PCA involvement had been identified as risk factors for an unfavorable social outcome in univariate analysis, only infarction present on preoperative images and PCA involvement remained statistically significant after multivariate adjustment.

Conclusions. Posterior cerebral artery involvement can be considered one of the underlying risk factors for unfavorable social outcome and should be studied further to improve social outcome in pediatric moyamoya disease.

(MOYAMOYA disease, characterized by progressive spontaneous occlusion of bilateral internal carotid arteries (ICAs) and development of abnormal collateral vessels, is one of the major causes of stroke in childhood. Surgical revascularization is believed to benefit pediatric patients with moyamoya disease. Such surgery is classified into 3 categories: direct, indirect, and combined bypass. While indirect bypass is more commonly applied to pediatric patients than direct or combined bypass, both types of surgery are equally effective for pediatric patients. Recent studies have reported favorable long-term results for both direct and indirect bypasses in terms of preventing strokes or transient ischemic attacks. However, social outcomes vary in terms of education and employment at adulthood, and a substantial portion of the patients suffer from social adaptation difficulties even after surgery. Although reports associate several factors with unfavorable social or functional outcomes, studies addressing this issue are lacking.

Involvement of a stenoocclusive lesion in the posterior circulation, especially in the posterior cerebral artery (PCA), is a relatively specific finding in juvenile-onset
moyamoya disease.\textsuperscript{19} The PCA usually provides much collateral flow to the anterior circulation in moyamoya disease, and recent studies revealed a higher prevalence of ischemic and hemorrhagic stroke in patients with such PCA involvement.\textsuperscript{7,22} However, any association between long-term outcomes and PCA involvement in moyamoya disease has not yet been closely examined.

We hypothesized that PCA involvement in pediatric moyamoya disease represents an underlying factor for poor social outcome. To test this hypothesis, we analyzed long-term follow-up data on consecutive patients who had survived at least 10 years after undergoing combined bypass surgery in childhood. Combined bypass surgery is superficial temporal artery (STA) to middle cerebral artery (MCA) anastomosis with encephalomyosynangiosis (EMS) Since the 1980s, our group has consistently adopted combined bypass as the first-choice treatment for pediatric patients with moyamoya disease.\textsuperscript{12,13} This was, to the best of our knowledge, the longest follow-up study among the previous reports on direct or combined bypass for pediatric moyamoya disease.\textsuperscript{3,6,11,13,16}

\section*{Methods}

\subsection*{Patient Population}

Between 1984 and 2003, the senior author (S.M.) performed combined bypass surgery on 61 pediatric patients with moyamoya disease at Kyoto University Hospital in Kyoto, Japan, and its satellite hospital. The senior author created a personal database by collecting data on these consecutive cases including patient identification number, age at admission, sex, age at symptom onset, primary clinical manifestations at onset, clinical condition at admission (translated later into the modified Rankin scale [mRS] score with age-specific modification\textsuperscript{23}), date and procedure of surgery, and angiographic findings upon each patient’s first or second admission. These patients were followed prospectively at our hospital. This study was approved by the ethics committee of the Kyoto University Graduate School of Medicine.

\subsection*{Diagnosis and Radiological Assessment}

Moyamoya disease was diagnosed in the patients according to criteria proposed by the Research Committee on Moyamoya Disease in Japan.\textsuperscript{4,28,34} The diagnoses were confirmed by cerebral angiography in all cases. Children with a typical occlusive finding in the unilateral ICA alone were also considered to have moyamoya disease.\textsuperscript{29} Children with autoimmune disease, meningitis, brain tumor, Down syndrome, neurofibromatosis Type 1, or a history of head irradiation were excluded from the present study.

For all patients, we recorded the presence and distribution of infarction before surgery as revealed through CT in early cases or MRI. The hemisphere in which infarctions was dominantly distributed and the presence of bilateral infarctions were also recorded. In cases in which either the original CT scans or MR images were preserved, one of the authors (T.F.) quantitatively assessed the size of infarction on preoperative images in which the patient name was hidden. The area of infarction was measured with Adobe Photoshop software through manual tracing of the lesion on the image slice with the maximum lesion size. If the targeted slice contained more than 2 lesions, the total area of all visible lesions was calculated.

Findings of all angiograms, which had first been reviewed by the senior author on patient admission, were checked again by a coauthor (K.Y.) who was blinded to all clinical information. Unilateral lesion of the ICA was defined as unilateral stenosis or occlusion of the terminal portion of the ICA with the formation of moyamoya vessels accompanied by no or a subtle lesion around the contralateral terminal portion of the ICA. The severity of disease progression in the ICA was evaluated with a 4-stage system,\textsuperscript{24} with a higher ICA stage representing more advanced stenoocclusive lesions in the anterior circulation. If the two hemispheres were classified as different ICA stages, the higher stage was recorded. Involvement of the PCA was defined as the presence of occlusion or stenosis greater than 50% in the P\textsubscript{1} to P\textsubscript{3} segment of either PCA (Fig. 1).

\subsection*{Treatment Protocol}

Surgical revascularization was indicated for patients with cerebral ischemic manifestations. Single photon emission computed tomography (SPECT) was performed in all but the first few cases to detect hemodynamic impairment, which was considered an indicator suggesting surgical revascularization. All patients underwent direct or combined bypass consisting of STA-MCA anastomosis with or without EMS in each MCA territory as a first-line treatment. Encephalomyosynangiosis, an indirect bypass procedure using the pedicle flap of the temporalis muscle, was usually combined with STA-MCA anastomosis for patients under 10 years of age. All surgeries were performed by the senior author (S.M.). Previously published studies detail the surgical procedure.\textsuperscript{13} Briefly, a horseshoe-shaped scalp incision is made surrounding the parietal branch of the STA, and the temporalis muscle is dissected along the horseshoe incision to make the pedicle flap. The dura is widely opened, preserving the main branch of the meningeal arteries. After a conventional...
procedure of STA-MCA single anastomosis, the pedicle flap of the temporalis muscle is placed over the brain surface and sutured to the edge of the remaining dura. For patients with bilateral ICA involvement, the more symptomatic or hemodynamically impaired side is revascularized first. The second revascularization for the contralateral MCA territory is performed at least 1 month after the first revascularization. To assess bypass patency and improvement of cerebral blood flow, angiography and SPECT were performed 3 months after the second revascularization. In most cases these bypasses widely covered the brain surface beyond the MCA territory.  If SPECT reveals insufficient hemodynamic improvement in the anterior or posterior cerebral artery territories, additional direct revascularizations are considered to the territories of the anterior cerebral artery (ACA) or PCA using the frontal branch of the STA or occipital artery.

**Follow-Up Data Collection**

All follow-up data were acquired through a medical interview and neurological examination at the outpatient neurosurgical clinic. The data obtained at the last visit were used for analysis. Transient ischemic attacks were classified into 4 categories by frequency: eliminated, rare (several times per year), frequent (several times per month or per week), or exacerbated after surgery. The mRS score for each patient was recorded. Late-onset stroke was defined as ischemic stroke or intracranial hemorrhage occurring more than 30 days after surgery, causing certain neurological symptoms, and identified by neuroradiological modalities.

The patients were interviewed about educational background, employment history, and current occupation. Educational background was assessed in all patients and classified by type of school: regular class at ordinary school, special class, or school for the disabled. Employment was assessed in all patients except homemakers and those currently enrolled as students. An unfavorable social outcome was defined as patient difficulty in either attending regular classes or obtaining regular employment.

**Statistical Analysis**

To compare baseline characteristics, a t-test, the Wilcoxon rank-sum test, or the Fisher exact test was used as appropriate. The mRS scores at the last follow-up evaluation and those at first admission were compared by means of the Wilcoxon signed-rank test. Variables including sex, age of onset, time interval between onset and first bypass surgery, presence of infarction in the preoperative image, infarction area, side of infarction, bilateral infarction, unilateral ICA lesion, ICA stage, involvement of the PCA, and late-onset stroke were incorporated into univariate analysis to identify factors associated with an unfavorable social outcome. The Fisher exact test and logistic regression analysis were used for univariate analysis. Variables with a p value < 0.1 on univariate analyses were selected for further multivariate analysis. The ICA stage was incorporated into multivariate analysis regardless of its p value in univariate analysis in light of the likelihood of correlation between ICA stage and PCA involvement.

Variables including missing data were not incorporated into multivariate analysis. Multiple logistic regression analysis was used for multivariate analysis. Two-sided p values < 0.05 were considered statistically significant. All statistical analyses were performed with JMP software (version 9, SAS Institute Inc.).

**Results**

**Patient Background**

Table 1 summarizes patient backgrounds before surgery. The female-to-male ratio was 1.3 to 1, and the median age at onset was 6 years (mean 6.5 years, range 0–15 years). No patient experienced intracranial hemorrhage at disease onset. At the time of first admission, 47 patients (77.0%) had an mRS score of 0, 6 (9.8%) a score of 1, 6 (9.8%) a score of 2, and 2 (3.3%) a score of 3. Involvement of the PCA was detected in 22 patients (36.1%).

Infarction, assessed preoperatively with CT in 25 patients (41.0%) and with MRI in 36 patients (59.0%), was detected in 34 patients (55.7%). At the time of retrospective assessment of the infarction area, the original image was not available in 8 of the 61 patients because of the expiration of the film storage period. The median and mean areas of preoperative infarction measured in the remaining cases were 6.4 mm² and 206.1 mm², respectively (range 0–1652.9 mm²).

**Surgery**

A total of 119 surgeries were performed for 61 patients. Table 2 summarizes the number of revascularization surgeries. All patients underwent at least 1 STA-MCA anastomosis. Forty-three patients (76.8%) underwent bypass surgeries twice, while 5 (8.2%) underwent additional revascularization to the ACA or PCA territory. One patient experienced a small infarction in the temporococcipital region immediately after STA-MCA anastomosis, resulting in transient disorientation but no permanent deficit. The patency of the bypasses was confirmed in all cases by means of postoperative angiography.

**Follow-Up**

The mean follow-up period (± SD) was 15.8 ± 7.0 years, and the mean age at last follow-up was 24.0 ± 6.8 years. Follow-up information was not available in 5 patients (8.2%): 2 were followed up by institutes outside Japan, and 3 were lost to follow-up when their attendant doctors in the outpatient clinic were transferred after surgery. The remaining 56 patients for whom follow-up data were acquired were assessed for further analysis. Baseline characteristics were not statistically different between patients with and without follow-up data (Table 1).

**Outcome**

Transient ischemic attacks were eliminated in 52 cases (92.9%) and rare in 4 (7.1%) during the follow-up period. Late-onset ischemic or hemorrhagic stroke occurred in 4 patients (7.1%). One patient suffered from acute subdural hematoma due to a traffic accident 33 months af-
PCA involvement and social outcome in moyamoya disease

**TABLE 1: Comparison of baseline characteristics of groups with and without follow-up data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Followed Up</th>
<th>Lost to Follow-Up</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>61</td>
<td>56</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>females (%)</td>
<td>35 (57.4)</td>
<td>33 (58.9)</td>
<td>2 (40.0)</td>
<td>0.642</td>
</tr>
<tr>
<td>mean age of admission in yrs ± SD</td>
<td>8.6 ± 3.7</td>
<td>8.7 ± 3.7</td>
<td>7.8 ± 3.1</td>
<td>0.596</td>
</tr>
<tr>
<td>mean age of onset in yrs ± SD</td>
<td>6.5 ± 3.5</td>
<td>6.6 ± 0.5</td>
<td>5.8 ± 1.5</td>
<td>0.629</td>
</tr>
<tr>
<td>median delay in yrs until surgery (IQR)</td>
<td>1 (0–3)</td>
<td>1 (0–3)</td>
<td>1 (0.5–4)</td>
<td>0.756</td>
</tr>
<tr>
<td>infarction on preop image (%)</td>
<td>34 (55.7)</td>
<td>32 (57.1)</td>
<td>2 (40.0)</td>
<td>0.647</td>
</tr>
<tr>
<td>median area in mm² (IQR)*</td>
<td>6.4 (0–156.0)</td>
<td>7.6 (0–167.9)</td>
<td>0 (0–128.5)</td>
<td>0.351</td>
</tr>
<tr>
<td>lt hemisphere infarction (%)</td>
<td>29 (47.5)</td>
<td>26 (46.4)</td>
<td>3 (60.0)</td>
<td>0.662</td>
</tr>
<tr>
<td>bilat infarction (%)</td>
<td>6 (9.8)</td>
<td>5 (8.9)</td>
<td>1 (20.0)</td>
<td>0.415</td>
</tr>
<tr>
<td>unilat ICA lesion (%)</td>
<td>6 (9.8)</td>
<td>6 (10.7)</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>ICA stage (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>7 (11.5)</td>
<td>6 (10.7)</td>
<td>1 (20.0)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>29 (47.5)</td>
<td>27 (48.2)</td>
<td>2 (40.0)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>23 (37.7)</td>
<td>21 (37.5)</td>
<td>2 (40.0)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>2 (3.3)</td>
<td>2 (3.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>≥III</td>
<td>25 (41.0)</td>
<td>23 (41.1)</td>
<td>2 (40.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>PCA involvement</td>
<td>22 (36.1)</td>
<td>21 (37.5)</td>
<td>1 (20.0)</td>
<td>0.645</td>
</tr>
</tbody>
</table>

* Data on the infarction area were not available in 8 of the 61 patients. IQR = interquartile range; NA = not applicable.

Table 2: Number of revascularization surgeries by type*

<table>
<thead>
<tr>
<th>Mode of Revascularization Surgery</th>
<th>No. of Surgeries</th>
</tr>
</thead>
<tbody>
<tr>
<td>STA-MCA anastomosis w/ EMS</td>
<td>97</td>
</tr>
<tr>
<td>STA-MCA anastomosis w/o EMS</td>
<td>13</td>
</tr>
<tr>
<td>STA-ACA bypass</td>
<td>2</td>
</tr>
<tr>
<td>OA-PCA bypass</td>
<td>1</td>
</tr>
<tr>
<td>other</td>
<td>6</td>
</tr>
</tbody>
</table>

* OA = occipital artery.

PCA involvement and STA-MCA anastomosis, which resulted in ischemic stroke in the affected hemisphere. Three patients suffered from intracranial hemorrhage at the mean age of 26 years (range 24–29 years). One patient experienced a second hemorrhage, which resulted in a fatal outcome. The overall incidence of late-onset stroke was not significantly associated with an unfavorable social outcome (Table 3). At the time of the last follow-up, 40 patients (71.4%) had an mRS score of 0, 5 (8.9%) a score of 1, 8 (14.3%) a score of 2, 2 (3.6%) a score of 3, and 1 (1.8%) a score of 6. Among the patients with follow-up, no significant difference in mRS scores was evident between first admission and last follow-up (p = 0.182).

Seven (18.9%) of 37 patients who were not currently students or homemakers encountered difficulty in obtaining regular employment. Six patients (10.7%) currently or previously attended special classes or a school for the disabled. In summary, 10 (17.9%) of 56 patients had an unfavorable social outcome: 4 had difficulty obtaining regular employment, 3 had difficulty attending regular classes, and 3 had both difficulties. Univariate analysis revealed that younger age at onset, longer delay between onset and surgery, infarction present in the preoperative image, and PCA involvement were significantly associated with an unfavorable outcome (Table 3). The area of infarction was also significantly larger in patients with an unfavorable outcome than in those with a favorable outcome, although the infarction area could not be measured in 7 of the patients with follow-up because original images were no longer available. Advanced ICA lesion (Stage III or IV), unilateral ICA lesion, left hemisphere infarction, and bilateral distribution of infarction were not significantly associated with outcome.

Variables including the age of onset, delay between onset and surgery, infarction present in the preoperative image, ICA stage, and PCA involvement were incorporated into a further multivariate analysis (Table 4). In this analysis, only infarction present on the preoperative image (OR 9.96, 95% CI 1.08–355.82) and PCA involvement (OR 7.44, 95% CI 1.22–67.79) were identified as significant factors associated with an unfavorable social outcome. The frequency of an unfavorable social outcome was stratified by PCA involvement and delay between onset and surgery to estimate the impact of the combination of these factors on social outcome. The frequency of an unfavorable social outcome reached 50% when PCA involvement and a surgical delay exceeding 3 years were combined, while that in patients with neither risk factor was 0% (Table 5).

**Discussion**

Despite the favorable long-term outcomes overall, our results reveal that 17.9% of pediatric patients with moyamoya disease continued to suffer from social adaptation difficulties as they matured, even after bypass surgery. The results also suggest that PCA involvement and presence of infarction on preoperative images are independently associated with an unfavorable social outcome.
Our results indicating that more than 80% of patients had a favorable social outcome appear comparable to those of past studies, in which the frequency of patients with a normal intelligence quotient or capable of independent daily activities remained 63.5%–87%. Nevertheless, our results, along with those of several pioneering studies, shed light on the salient issue of social adaptation in pediatric moyamoya disease. Nakashima et al. reported that approximately 10% of patients had severe difficulty in social or school life because of intellectual impairment. While Phi et al. reported good long-term social outcomes in terms of education and employment, their results also revealed that a certain proportion of patients had difficulty planning their marriages and acquiring driver’s licenses, and that approximately 20% of the respondents were dissatisfied with their treatment outcomes.

Several factors, including preoperative neurological impairment,10,17,29 infarction,13,14 age of symptom onset,10,13 and duration after onset,9 have been reported as affecting social or functional outcomes. Our result in univariate analysis is consistent with these reports. In addition, our result in multivariate analysis suggests that PCA involvement, which has so far received less attention in long-term follow-up studies, is also an independent risk factor for unfavorable social outcomes. Involvement of the PCA is more likely to occur in younger children19,22 and thus may act as a potential confounder affecting social outcome in the previous studies. Although several studies reported that PCA involvement is associated with a high prevalence of preexisting infarction at diagnosis,22,23 our results from the multivariate analysis suggest that both the preexisting infarction and PCA involvement are independently associated with an unfavorable social outcome. We speculate on several possible reasons why PCA involvement is associated with unfavorable social outcomes. Involvement of the PCA may more accurately represent the overall progression of a stenoocclusive lesion in pediatric moyamoya disease.20,23 The other possible explanation is that PCA involvement may cause further reduction in cerebral blood flow because the PCA usually provides important collateral flow to the affected anterior circulation via leptomeningeal anastomosis in patients with moyamoya disease. In particular, a pair of posterior pericallosal arteries, branches of the PCA, is well developed in moyamoya disease as a collateral pathway to the medial frontal cortex. The medial frontal cortex involves various executive, emotional, and behavioral functions,33 and decreased cerebral blood flow in this area may impede social adaptation abilities even with minimal infarct. Interestingly, Nakagawara et al. speculated that long-standing mild hemodynamic ischemia in the medial frontal lobe could lead to selective neuron loss detected by SPECT imaging with benzodiazepine receptor radioligand, and cognitive dysfunction in patients with moyamoya disease.26

Our study has some limitations. First, the result of our multivariate analysis has a relatively large confidence interval, which can be attributed to the limited number of cases. However, the baseline characteristics of this study, outcome in the previous studies. Although several studies reported that PCA involvement is associated with a high prevalence of preexisting infarction at diagnosis,22,23 our results from the multivariate analysis suggest that both the preexisting infarction and PCA involvement are independently associated with an unfavorable social outcome.

### TABLE 3: Univariate analyses for factors associated with long-term social outcome in all patients with follow-up*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Favorable Outcome (n = 46)</th>
<th>Unfavorable Outcome (n = 10)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>female</td>
<td>26 (56.5)</td>
<td>7 (70.0)</td>
<td>0.500</td>
</tr>
<tr>
<td>mean age of onset in yrs ± SD</td>
<td>7.1 ± 3.6</td>
<td>4.1 ± 1.8</td>
<td>0.021</td>
</tr>
<tr>
<td>median delay until surgery in yrs (IQR)</td>
<td>1 (0–2)</td>
<td>3 (1.5–9.25)</td>
<td>0.015</td>
</tr>
<tr>
<td>infarction on preop image</td>
<td>23 (50.0)</td>
<td>9 (90.0)</td>
<td>0.021</td>
</tr>
<tr>
<td>median area in mm² (IQR)†</td>
<td>0 (0–67.9)</td>
<td>370.1 (58.8–1220.5)</td>
<td>0.028</td>
</tr>
<tr>
<td>lt hemisphere infarction</td>
<td>20 (43.5)</td>
<td>6 (60.0)</td>
<td>0.487</td>
</tr>
<tr>
<td>bilat infarction</td>
<td>3 (6.5)</td>
<td>2 (20.0)</td>
<td>0.214</td>
</tr>
<tr>
<td>unilat ICA lesion</td>
<td>6 (13.0)</td>
<td>0 (0)</td>
<td>0.578</td>
</tr>
<tr>
<td>ICA stage ≥3</td>
<td>17 (37.0)</td>
<td>6 (60.0)</td>
<td>0.288</td>
</tr>
<tr>
<td>PCA involvement</td>
<td>13 (28.3)</td>
<td>8 (80.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>overall late-onset stroke</td>
<td>2 (4.4)</td>
<td>2 (20.0)</td>
<td>0.142</td>
</tr>
</tbody>
</table>

* All data given as number of patients (%) unless otherwise indicated.
† Data regarding the infarction area were not available in 7 of the 56 patients with follow-up.

### TABLE 4: Multivariate analyses for factors associated with unfavorable long-term social outcome in all patients with follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>p Value</th>
<th>Adjusted OR (95% CI) for Unfavorable Social Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean age of onset</td>
<td>0.122</td>
<td>0.80 (0.58–1.06) for every yr</td>
</tr>
<tr>
<td>median delay until surgery</td>
<td>0.118</td>
<td>1.32 (0.94–2.03) for every yr</td>
</tr>
<tr>
<td>infarction on preop image</td>
<td>0.042</td>
<td>9.96 (1.08–355.82)</td>
</tr>
<tr>
<td>ICA stage ≥3</td>
<td>0.704</td>
<td>0.67 (0.07–5.11)</td>
</tr>
<tr>
<td>PCA involvement</td>
<td>0.029</td>
<td>7.44 (1.22–67.79)</td>
</tr>
</tbody>
</table>

### TABLE 5: Frequency of unfavorable social outcomes stratified by PCA involvement and delay until bypass surgery

<table>
<thead>
<tr>
<th>Length of Delay (yrs)</th>
<th>Without PCA Involvement</th>
<th>With PCA Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>0</td>
<td>30.8%</td>
</tr>
<tr>
<td>≥3</td>
<td>28.5%</td>
<td>50.0%</td>
</tr>
</tbody>
</table>

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T. Funaki et al.
PCA involvement and social outcome in moyamoya disease

such as peak age of onset and female-to-male ratio, were similar to those in previous large epidemiology studies.1,15,38

Our sample thus can be considered reflective of the general population of pediatric patients with moyamoya disease. Second, our analysis did not include 8.2% of patients because of loss of follow-up, which could cause a certain bias if the trends of these patients differed significantly from those of the analyzed patients. Given that the baseline characteristics did not differ statistically between patients with and without follow-up data, however, such bias is likely minimal. Third, whether our results can be generalized to patients treated with an indirect bypass, such as encephalo-duroarteriosynangiosis, is debatable. Generalization of our results may be partially allowed because recent reviews show that direct and indirect bypasses are equally effective over the long term.5,30,35

Viewed from a practical perspective, early revascularization may be required for patients with PCA involvement because the risk of an unfavorable social outcome markedly increases with the combination of PCA involvement and a delay in surgical treatment (Table 5). An aggressive revascularization strategy to the PCA or even ACA territory can also be proposed for patients with PCA involvement. A more recent study revealed that a stenoocclusive lesion of the PCA could progress even after surgery and reduce cerebral blood flow.8 Careful follow-up is needed to minimize an unfavorable social outcome after bypass surgery of pediatric moyamoya disease.

Conclusions

The results of the present study support the hypothesis that the involvement of a stenoocclusive lesion in the PCA is one of the possible risk factors for an unfavorable social outcome from pediatric moyamoya disease. The finding of PCA involvement in pediatric moyamoya disease should receive more attention to ensure further improvement in social outcomes at adulthood.

Acknowledgment

We appreciate the efforts of Yuko Tanaka in collecting patient records.

Disclosure

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 to the study and manuscript preparation include the following. Conception and design: Funaki. Acquisition of data: Funaki. Analysis and interpretation of data: Funaki. Drafting the article: Funaki. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Funaki. Statistical analysis: Funaki.

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