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Prediction of the Clinical Outcome of Pediatric Moyamoya Disease With Postoperative Basal/Acetazolamide Stress Brain Perfusion SPECT After Revascularization Surgery

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Background and Purpose—We evaluated whether basal/acetazolamide stress brain perfusion SPECT performed after revascularization surgery can predict the further clinical outcome of patients with pediatric moyamoya disease.

Methods—A total of 77 (31 males, 46 females, age 6.6 ± 3.2 years) patients with postoperative pediatric moyamoya disease who underwent basal/acetazolamide stress brain perfusion SPECT 6 to 12 months after revascularization surgery and who were followed-up >12 months after SPECT were included. Mean follow-up period after SPECT was 36 ± 19 months. Sixty-two patients underwent bilateral ribbon encephaloduroarteriosynangiosis (EDAS), 14 bilateral EDAS, and 1 unilateral EDAS. Ordinal logistic regression analysis using 5 independent variables (infarction on preoperative MRI, age at the first operation, highest Suzuki stage on cerebral angiography, and regional cerebrovascular reserve on postoperative SPECT) against postoperative clinical outcomes was performed.

Results—Fifty-one patients had preserved reserve on postoperative SPECT and their clinical outcomes were excellent (30), good (15), fair (4), and poor (2); 26 patients had decreased reserve (excellent, 1; good, 7; fair, 14; poor, 4). On ordinal logistic regression analysis, age at the first operation ($P=0.033$) and reserve on postoperative SPECT ($P<0.001$) were statistically significant.

Conclusion—Basal/acetazolamide stress brain perfusion SPECT performed at 6 to 12 months after the indirect bypass operation could predict the further clinical outcome of pediatric patients with moyamoya disease. Patients with decreased cerebrovascular reserve will have remaining neurological deficit and ischemic attacks on follow-up. (*Stroke*. 2005;36:1485-1489.)

Key Words: cerebral revascularization ■ moyamoya disease ■ outcome ■ tomography, emission, computed

Moyamoya disease is a progressive occlusive cerebrovascular disease of the internal carotid arteries or their branches with compensatory development of a fine collateral vascular network at the base of the brain (moyamoya vessels).^{1,2} For the diagnosis and evaluation of the moyamoya disease, cerebral angiography and MRI are usually performed.³

Basal/acetazolamide stress brain perfusion SPECT performed in pediatric moyamoya disease patients can disclose regions of decreased cerebral perfusion and cerebrovascular reserve, which can be improved by revascularization surgery, ie, indirect bypass operation.^{4–6}

Known prognostic factors for pediatric moyamoya disease after operation are preoperative multiple cerebral infarctions, early onset at a young age, perioperative complications such as ischemic events, high Suzuki stages on cerebral angiography, and surgical procedure itself.^{7–11} In our institute, basal/acetazolamide stress brain perfusion SPECT is performed for preoperative and postoperative evaluation of pediatric moyamoya disease

patients.^{5,6,11} In this study, we evaluated whether basal/acetazolamide stress brain perfusion SPECT performed after the indirect bypass operation can predict the further clinical outcomes of pediatric moyamoya disease patients.

Materials and Methods

Patients

The indirect bypass operation for pediatric moyamoya disease patients started in 1987 at our institute. Most patients were treated with encephaloduroarteriosynangiosis (EDAS) until October 1995, and after that time most patients were treated with EDAS with bifrontal encephalogaleo(periosteal)synangiosis (ribbon EDAS).^{6,12} Basal/acetazolamide stress brain perfusion SPECT began in 1995. From 1987 to 2000, 201 pediatric moyamoya disease patients underwent indirect bypass operation, ie, EDAS or ribbon EDAS on involved cerebral hemispheres, with one side being followed by the other side. Among these 201 patients, 77 patients who satisfied the following criteria were enrolled in this study: (1) patients with bilateral ($n=76$) or unilateral ($n=1$) disease who underwent indirect bypass operation in the involved cerebral hemispheres; (2) patients in

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TABLE 1. Clinical Characteristics of 77 Patients

	No. of Patients		
	Decreased rCVR (n=26)	Preserved rCVR (n=51)	Total (n=77)
Age			
Mean±SD (range)	5.8±3.0 y (7 mo to 14 y)	7.0±3.3 y (1 to 14 y)	6.6±3.2 y
Sex			
Male:Female	10:16	21:30	31:46
Highest Suzuki stages (%)			
I	1 (4)	1 (2)	2 (3)
II	1 (4)	12 (24)	13 (17)
III	12 (46)	25 (49)	37 (48)
IV	11 (42)	11 (22)	22 (29)
V	1 (4)	2 (4)	3 (4)
VI	0	0	0
Cerebral infarction on preoperative MRI (%)	17 (65)	26 (53)	43 (56)
Operative procedures			
Bilateral EDAS (%)	4 (15)	11* (22)	15* (19)
Bilateral ribbon EDAS (%)	22 (85)	40 (78)	62 (81)
Follow-up angiography	n=33 hemispheres	n=68 hemispheres	n=101 hemispheres
Improved (%)	16 (49)	44 (65)	60 (59)
No change (%)	10 (30)	16 (24)	26 (26)
Aggravated (%)	7 (21)	8 (12)	15 (15)

EDAS indicates encephaloduroarteriosynangiosis; rCVR, regional cerebrovascular reserve on postoperative basal/acetazolamide stress brain perfusion SPECT; ribbon EDAS, EDAS with bifrontal encephalogaleo(perioosteal)synangiosis.

*One patient underwent unilateral EDAS because of unilateral disease.

whom basal/acetazolamide stress brain perfusion SPECT was performed 6 to 12 months after the last operation; and (3) patients whose post-SPECT follow-up periods were ≥ 12 months. Nine patients who had perioperative complications were excluded from this study.

Male-to-female ratio was 31:46, and the age (mean±SD) at the first operation was 6.6 ± 3.2 years (range, 7 months to 14 years). Forty-three patients had cerebral infarction on their preoperative MRI. Sixty-two patients underwent bilateral ribbon EDAS and 14 patients underwent bilateral EDAS without ribbon; one patient underwent unilateral EDAS because of unilateral disease. Suzuki stages of cerebral angiography of 153 involved cerebral hemispheres were as follows: stage 1, 8 hemispheres; stage 2, 32 hemispheres; stage 3, 72 hemispheres; stage 4, 36 hemispheres; stage 5, 5 hemispheres; stage 6, 0 hemispheres. The follow-up period after postoperative SPECT was 36 ± 19 months (mean±SD; range, 12 to 90 months). Clinical characteristics of patients are summarized in Table 1.

Basal/Acetazolamide Stress Brain Perfusion SPECT

Chloral hydrate syrup was used for the sedation of patients. For basal study, 9.25 MBq/kg of ^{99m}Tc -hexamethylpropyleneamine oxime (HMPAO; Amersham, Buckinghamshire, England) was intravenously injected and the acquisition started 5 minutes after. Ten minutes before the end of basal SPECT acquisition, 20 mg/kg of acetazolamide was injected intravenously. Five minutes after the end of basal study acquisition, 18.5 MBq/kg of ^{99m}Tc -HMPAO was injected, and the acquisition of stress study began 5 minutes after. Total procedure took ≈ 45 minutes.⁵ Acetazolamide stress images were obtained by decay-corrected subtraction of basal images from the corresponding stress images.

A triple-head gamma camera (Prism 3000; Picker International) with a low-energy high-resolution fan beam collimator was used for acquisition. Forty step-and-shoot images per detector were acquired with intervals of 3° for 20 seconds per each step. The SPECT images

were reconstructed with filtered back projection using a Metz filter on 128×128 matrix.¹³

Two nuclear physicians who were unaware of patients' medical records performed visual interpretation of the SPECT images. Cerebellums were considered as the reference regions for visual inspection of basal and acetazolamide stress brain perfusion SPECT images. The SPECT images were assessed as either "preserved" or "decreased" regional cerebrovascular reserve (rCVR). Decreased rCVR was defined as cerebral perfusion of acetazolamide stress SPECT that fell into a lower color range from basal SPECT over at least one-third of any brain lobe.

Assessment of Postoperative Clinical Outcomes

The postoperative clinical outcome of each patient was assigned to one of the following 4 categories on the last follow-up by their neurosurgeons: (1) excellent, the preoperative symptoms such as transient ischemic attacks have totally disappeared without fixed neurological deficits; (2) good, the symptoms have totally disappeared but the neurological deficits remained; (3) fair, the symptoms persisted but their frequency has decreased; and (4) poor, the symptoms remained unchanged or worsened.^{6,11}

Quantitative Analysis

To show the confidence of the visual finding, vascular reserve in the lesions was quantified and compared with the results of the visual analysis. Region of interest was drawn on the area with decreased perfusion and reference region (cerebellums). The count of lesion was normalized to the counts of cerebellums. With these normalized counts, we calculated the cerebral vascular reserve index (CVRI) using the following equation:

$$CVRI = \frac{C_{\text{acetazolamide}} - C_{\text{basal}}}{C_{\text{basal}}} \times 100 (\%)$$

where $C_{\text{acetazolamide}}$ and C_{basal} are the normalized counts in acetazolamide and basal SPECT images, respectively.¹³

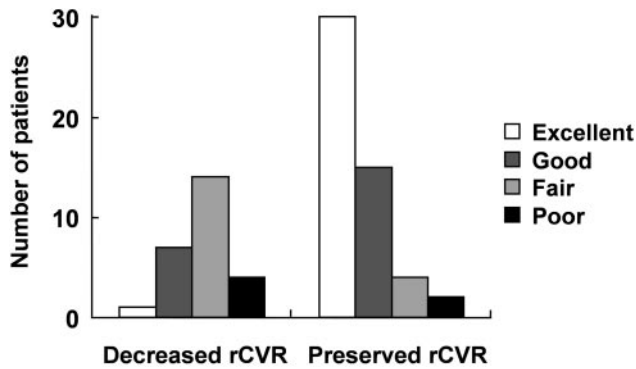


Figure 1. Regional cerebrovascular reserve (rCVR) on postoperative SPECT vs further clinical outcomes of total 77 patients. Patients with preserved rCVR on postoperative brain perfusion SPECT had more favorable postoperative clinical outcomes (excellent, good) compared with those with decreased rCVR.

Follow-up Cerebral Angiography

Follow-up cerebral angiography was performed on 101 cerebral hemispheres among 153 involved hemispheres 17±15 months after indirect bypass operation. Follow-up angiography was performed on 33 hemispheres among 52 involved hemispheres of 26 patients with decreased rCVR and on 68 hemispheres among 101 involved hemispheres of 51 patients with preserved rCVR. The improvement, no change, or aggravation was determined on follow-up angiography in comparison with the Suzuki stages of preoperative angiography.

Statistical Analysis

Ordinal logistic regression was used for the analysis of total 77 patients. Cerebral infarction on preoperative MRI, age at the first operation, the highest Suzuki stage of cerebral angiography, operative procedure (EDAS or ribbon EDAS), and rCVR on postoperative SPECT (preserved or decreased) were considered as independent variables; postoperative clinical outcome was considered as a dependent variable. We used SPSS 12.0 for windows.

Student *t* test was used in the comparison of CVRI between the patients with decreased and preserved vascular reserve in visual analysis. The χ^2 test was used in the comparison of results of follow-up angiography between the patients with decreased and preserved vascular reserve and also between the patients with excellent, good, fair, and poor outcomes.

For all tests, $P < 0.05$ was considered statistically significant.

Results

Postoperative clinical outcomes of total 77 patients were as follows: excellent, 31; good, 22; fair, 18; and poor, 6. Among 77 patients, postoperative clinical outcomes of 51 patients with preserved rCVR on postoperative SPECT were excellent (30), good (15), fair (4), and poor (2); those of 26 patients with decreased rCVR were excellent (1), good (7), fair (14), and poor (4; Figure 1).

In the quantitative analysis, the patients who showed the decreased vascular reserve in the visual analysis had significantly lower CVRI ($-8.9 \pm 5.0\%$) than the patients who showed preservation of vascular reserve in visual analysis ($-2.4 \pm 5.5\%$; $P < 0.001$; Figures 2 and 3).

On ordinal logistic regression analysis, age at the first operation ($P = 0.033$) and rCVR on postoperative SPECT ($P < 0.001$) were statistically significant prognostic factors for further clinical outcome, whereas cerebral infarction on preoperative MRI ($P = 0.213$), the highest Suzuki stage ($P = 0.479$), and operative procedure ($P = 0.371$) were not (Table 2).

TABLE 2. Ordinal Logistic Regression Analyses for the Postoperative Clinical Outcomes of Patients

Variable	P
Infarction on preoperative MRI	0.213
Age at the first operation	0.033
Highest Suzuki stage	0.479
rCVR on postoperative SPECT	0.000
Operative procedure	0.371

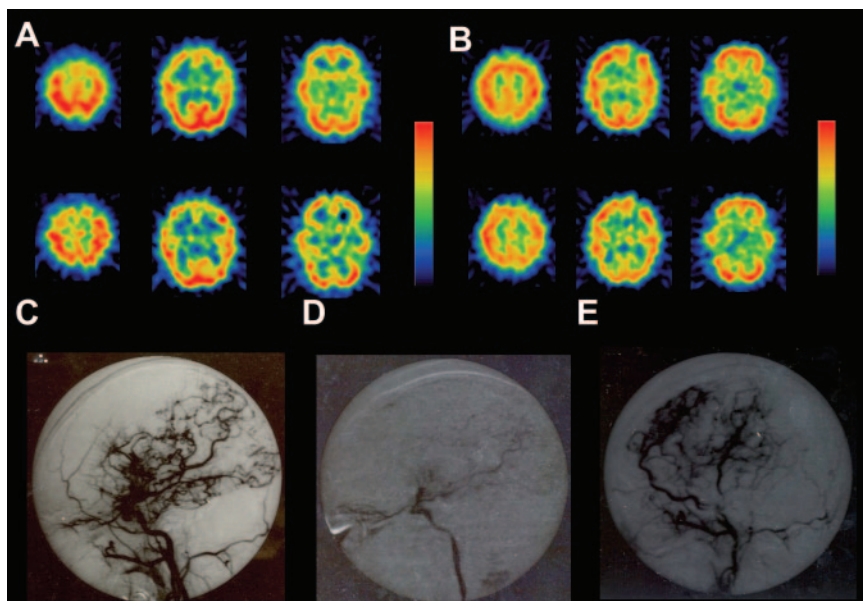
On follow-up angiography, among 101 cerebral hemispheres studied, 60 showed improved, 26 showed no change, and 15 had aggravated Suzuki stages. There was no significant difference of the changes of Suzuki stages among 33 hemispheres with decreased rCVR and 68 hemispheres with preserved rCVR ($P = 0.26$) (Table 1). There was also no significant difference of the changes of Suzuki stages among the patients with excellent, good, fair, and poor outcomes ($P = 0.62$).

Discussion

Pediatric moyamoya disease patients usually present with a transient motor weakness induced by hyperventilation. As patients blow on a toy or hot food, or cry, transient cerebral ischemia is caused by vasoconstriction secondary to a decreased arterial partial pressure of carbon dioxide. In addition to these transient problems, moyamoya disease patients have developmental delay in intelligence.¹⁴ Moyamoya disease is a unique cerebrovascular disease in that revascularization surgery can effectively prevent ischemic events and thus improve the long-term clinical outcome.^{15,16} Neurologic deficit and transient ischemic attacks are expected to be abolished, cognitive developments is expected to be normalized, and intelligence is expected to be improved after successful bypass surgery.^{15–17} This can happen because successful revascularization surgery is accompanied by catch-up growth and functioning of brain with normalized perfusion with ample perfusion reserve.

In this study, we found that pediatric patients with moyamoya disease who had decreased reserve still on postoperative basal/acetazolamide brain SPECT resulted in worse postoperative clinical outcomes. Though patients had underwent successful revascularization surgery on both cerebral hemispheres, decreased reserve on postoperative SPECT warrants close follow-up because these patients might need further intervention such as reoperation. Functional success accompanying successful anatomical revascularization could be diagnosed by cerebral perfusion and reserve on basal/acetazolamide brain SPECT in this study. Basal/acetazolamide brain perfusion SPECT performed at 6 to 12 months after the last revascularization surgery was chosen, because neovascularization in these hemispheres usually reaches a peak several months after the operation.^{18–20}

Various preoperative markers were reported to predict poorer postoperative outcome, but postoperative functional status of brain perfusion or reserve might influence further clinical outcome of these patients. In our analysis, as well as the early onset at a young age, decreased reserve on postoperative SPECT was a significantly poorer prognostic factor for further clinical outcome. However, the evidence of



bral angiography of right common carotid artery shows multiple moyamoya vessels at the middle cerebral artery territory. D, Postoperative cerebral angiography of right internal carotid artery performed 3 years after revascularization surgery shows markedly decreased moyamoya vessels. E, Postoperative cerebral angiography of right external carotid artery shows well-developed collateral vessels.

cerebral infarction on preoperative MRI, higher Suzuki grade on cerebral angiography, and operative procedure were not significant prognostic factors in our patient cohort. This is in contrast to our previous report that ribbon EDAS was more effective compared with simple EDAS in terms of clinical and functional outcome.⁶ This difference may be caused by the fact that among 77 patients only 15 patients underwent simple EDAS, whereas most of the patients underwent ribbon EDAS. Those who underwent simple EDAS underwent operation before the adoption of the basal/acetazolamide brain SPECT in our institution. Because patients with remaining neurological deficits without ischemic symptoms after

operation were classified as having “good” clinical outcome, most of the patients with preserved rCVR who had cerebral infarction on preoperative MRI were classified as having “good” outcome group. This might be the reason why the evidence of cerebral infarction on preoperative MRI was not a significant prognostic factor in this study.

In pediatric patients with moyamoya disease, intellectual functions usually begin deteriorating after the onset of the first neurological symptoms.¹⁴ Revascularization surgery was found to prevent this deterioration of intellectual functions by improving the cerebral blood flow.^{16,17} A subgroup of 21 patients performed preoperative and postoperative intelli-

Figure 2. Case with preserved rCVR on postoperative SPECT and excellent clinical outcome at 44 months after operation (36 months after SPECT). She underwent bilateral ribbon EDAS operation because of recurrent paraparesis attacks of both legs. Her preoperative Suzuki stage on cerebral angiography was 3/3 (right/left). A, Preoperative basal (top)/acetazolamide (bottom) brain perfusion SPECT showed decreased regional perfusion and rCVR on both frontotemporal cortices. Her preoperative full-scale intelligence quotient (FSIQ) was 96. B, Postoperative basal (top)/acetazolamide (bottom) brain perfusion SPECT acquired 6 months after completion of revascularization showed small perfusion defect on left anterior border zone caused by perioperative ischemic event but the rCVR was preserved on both cerebral hemispheres. The CVRI was 2.7%. Her symptom was resolved after operation. Her postoperative FSIQ measured at 3 years after postoperative SPECT was 120. C, Preoperative cere-

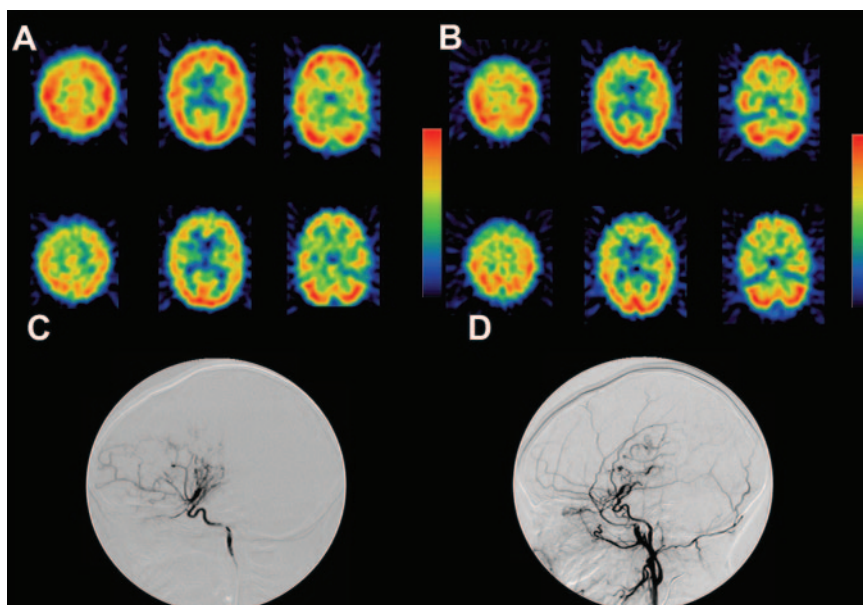


Figure 3. Case with decreased rCVR on postoperative SPECT and fair clinical outcome at 30 months after operation (18 months after SPECT). He underwent bilateral ribbon EDAS operation because of recurrent left paraparesis attacks. His preoperative Suzuki stage on cerebral angiography was 3/3 (right/left). A, Preoperative basal (top)/acetazolamide (bottom) brain perfusion SPECT showed decreased regional rCVR on right frontal cortex and left anterior frontal cortex. His preoperative FSIQ was 101. B, Postoperative basal (top)/acetazolamide (bottom) brain perfusion SPECT acquired 1 year after completion of revascularization showed small perfusion defect on right inferior frontal cortex and still decreased rCVR on right frontal cortex. His CVRI was -7.4%. His symptom persisted and his postoperative FSIQ at the same period was 84. C, Preoperative cerebral angiography of right internal carotid artery shows near-total occlusion of right middle cerebral artery with moyamoya vessels. D, Postoperative cerebral angiography of right common carotid artery performed 6 months after revascularization surgery shows poorly developed collateral vessels.

moya vessels. D, Postoperative cerebral angiography of right common carotid artery performed 6 months after revascularization surgery shows poorly developed collateral vessels.

gence tests according to the Korean Educational Development Institute Wechsler Intelligence Scale for Children (KEDI-WISC). Of these 21 patients, the mean full-scale intelligence quotient of 15 patients with preserved rCVR on their postoperative SPECT increased after revascularization surgery, and that of 6 patients with decreased rCVR on postoperative SPECT decreased. Because the results of intelligence tests were consistent with their postoperative clinical outcome in these 21 patients, decreased rCVR on postoperative SPECT warrants further intervention such as reoperation.

We used quaternary outcome at the last follow-up. The follow-up period varied from 12 to 90 months. Though we believe that survival analysis with event-free period would have been possible, the neurological deficit was not a once-and-for-all event during follow-up, but instead intermittent with very mild to severe degrees. Subjects sometimes needed clinical attention. However, there still remains the possibility to subdivide the "decreased or preserved" rCVR into extent and areas involved. Semiquantitative or quantitative evaluation of decreased rCVR and the pursuit of the correlation with the frequency/severity of ischemic events would be interesting. In acetazolamide-challenged SPECT, HMPAO might not reveal the subtle compromise of perfusion reserve caused by poor linearity in highly perfused areas because the uptake of highly perfused cerebellums could be underestimated compared with the regions of interest. Therefore, normalized counts of the regions of interest in acetazolamide-challenged HMPAO images could have higher values than that in basal images, which might result in small positive values in some areas of preserved rCVR.

Follow-up angiography results of patients analyzed against rCVR of SPECT did not show statistically significant difference between patients with decreased rCVR and patients with preserved rCVR, nor did they between patients with different postoperative clinical outcomes. Because this study is focused on the role of postoperative SPECT of pediatric moyamoya patients, difference of time point among postoperative SPECT, postoperative clinical outcome, and follow-up angiography may be the reason for no significance. Postoperative clinical outcome was assessed 36 ± 19 months after postoperative SPECT, which was performed 6 to 12 months after indirect bypass operation; follow-up angiography was performed 17 ± 15 months after indirect bypass operation.

In this simplified investigation, because we found that postoperative compromise in perfusion reserve was a foreboding for future ischemic attacks, we suggest that another helpful intervention such as reoperation should be conceived in this group of postoperative patients based on the basal/acetazolamide stress brain perfusion SPECT.

Summary

Basal/acetazolamide brain perfusion SPECT performed at 6 to 12 months after the completion of indirect bypass operation of the involved cerebral hemispheres could predict the further clinical outcomes of pediatric patients with moyamoya disease patients.

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