Research Square

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Non-Invasive Assessment of Angiogenesis Using Slab MIP Images in 3D TOF MRA Following Revascularization Surgery in Pediatric Moyamoya Disease

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Abstract

Purpose:

Evaluation of angiogenesis and cerebral circulation after revascularization is essential in pediatric moyamoya disease, but conventional methods such as digital subtraction angiography (DSA) and single-photon emission computed tomography (SPECT) are invasive and unsuitable for repeated follow-up. We aimed to develop an objective scoring index based on slab maximum intensity projection (MIP) images obtained from three-dimensional time-of-flight (3D TOF) magnetic resonance angiography (MRA) and to examine its correlation with DSA findings and cerebral blood flow (CBF) changes after surgery.

Methods:

We retrospectively analyzed 45 hemispheres in 28 pediatric patients who underwent revascularization between 2010 and 2023. Cortical angiogenesis was evaluated using slab MIP images before and after surgery, and scored using a modified Alberta Stroke Program Early CT Score (moya-ASPECTS). Associations with Matsushima grade, CBF and cerebrovascular reserve (CVR) measured by SPECT, and regression of moyamoya vessels were assessed.

Results:
The moya-ASPECTS score showed a strong correlation with Matsushima grade ($P < 0.001$). Postoperative resting CBF increased by 2.27 ml/100 g/min for each point increase in moya-ASPECTS (95% CI 0.87–3.67, $P = 0.003$). While moya-ASPECTS was not associated with CVR change, it correlated significantly with regression of moyamoya vessels (RR 1.33, 95% CI 1.12–1.58, $P < 0.001$). Higher moya-ASPECTS scores were inversely associated with postoperative asymptomatic infarction, although the number of events was small.

Conclusion:
The moya-ASPECTS score derived from slab MIP images provides a non-invasive, repeatable, and semi-quantitative method for evaluating postoperative cortical collateral formation in pediatric moyamoya disease. This method correlates well with DSA and CBF improvement, offering a practical alternative for long-term outpatient follow-up.

Introduction

Indirect bypass plays a dominant role in revascularization in patients with Moyamoya disease.[1,2] However, it is difficult to evaluate the development of blood supply using a method other than digital cerebral angiography (DSA) after indirect bypass in patients with Moyamoya disease, in contrast to direct bypass in patients with atherosclerotic occlusions. Therefore, DSA and single-photon emission computed tomography (SPECT) are the gold standard methods for evaluation after bypass surgery in patients with moyamoya disease.

The Matsushima classification based on DSA is the consensus approach for the evaluation of revascularization in moyamoya disease.[3] However, DSA is not suitable for observation over time because it requires hospitalization and is invasive and difficult to repeat. Since magnetic resonance angiography (MRA) is noninvasive and can be repeated on an outpatient basis, it is potentially useful for the evaluation of revascularization after bypass surgery in patients with moyamoya disease. MRA maximum intensity projection (MIP) images[4,5] may be used for this purpose, but they are subject to the bias of the radiologist in the creation of images. In contrast, slab MIP images obtained from 3D TOF MRA are objective because the radiologist does not influence their creation.[6] Thus, in this study, we examined the objective grading of revascularization using slab MIP images from 3D TOF MRA.

Patients and Methods

Study Design and Ethical Approval

This retrospective study was conducted at Yamaguchi University Hospital. The study protocol was reviewed and approved by the Institutional Review Board of Yamaguchi University Hospital (approval numbers H2020-095-4 and H2021-044-4). All patients and their families were informed of the study objectives, methods, and potential risks and provided written informed consent for surgical treatment and for the use of their clinical and imaging data for research and publication.

Patient Population

Between 2010 and 2023, 28 pediatric patients (14 boys and 14 girls; median age, 8.3 years [IQR, 6–10]; range, 4–16 years) diagnosed with moyamoya disease, including 2 cases of quasi-moyamoya disease, underwent revascularization surgery. A total of 45 hemispheres were analyzed. All diagnoses were based on the diagnostic and treatment guidelines issued by the Research Committee of the Ministry of Health, Labour, and Welfare, Japan.7,8 Most treated hemispheres presented with ischemic symptoms, including transient ischemic attacks or cerebral infarction, whereas two hemispheres were asymptomatic but showed insufficient cerebral circulation.

Surgical Procedures

Surgery was performed in the symptomatic hemisphere. The standard procedure consisted of superficial temporal artery to middle cerebral artery (STA–MCA) anastomosis combined with encephalo-durosynangiosis (EDS)[9] and encephalo-galeosynangiosis (EGS). If the MCA recipient branches were too small for direct anastomosis, encephaloduroarteriosynangiosis (EDAS) was combined with EDS and EGS. For patients with bilateral ischemic symptoms or insufficient cerebral circulation, surgery was performed on the contralateral side after an interval of six months to three years.

Imaging Acquisition and Processing

MRI was performed using a MAGNETOM Avanto 1.5T (2010–2023), MAGNETOM Skyra 3.0T (2010–present), or MAGNETOM Prisma 3.0T (2015–present) scanner (Siemens Medical Solutions, Forchheim, Germany) with a 32-channel head coil. Three-dimensional time-of-flight (3D TOF) MRA was performed with the following parameters: repetition time, 20 ms; echo time, 3.7 ms; flip angle, 20°; slice thickness, 0.7 mm; field of view, 220 × 172 mm; matrix, 384 × 300; pixel size, 0.57 × 0.57 mm. The imaging field extended from the foramen magnum to parietal convexity. The acquired data were reformatted as slab MIP images in an axial plane and displayed as 5-mm-thick overlapping slabs.

Evaluation of Neovascularization

To evaluate cortical angiogenesis, pre- and postoperative slab MIP images were reviewed side-by-side. Cortical angiogenesis was scored using a modified Alberta Stroke Program Early CT Score (ASPECTS), termed the moya-ASPECTS, ranging from 0 to 6 according to the distribution of cortical collaterals in the MCA cortical surface areas (M1-M6) (Fig. 1a). Each cortical region was assigned 1 point when cortical collateral vessels were identified in that region on slab MIP images. Thus, a score of 6 indicated the presence of cortical collaterals in all six cortical regions, whereas a score of 1 indicated their presence in only one region (Fig. 1b). Pre- and postoperative images were reviewed side-by-side to assess the extent and distribution of cortical collaterals and to evaluate interval changes after surgery.

Regression of moyamoya vessels was assessed on the same images and was classified as unchanged, < 50% regression, or > 50% regression. Similarly, the diameters of the superficial temporal artery (STA) and middle meningeal artery (MMA) were classified as unchanged, increased by < 50%, or increased by > 50% using pre- and postoperative slab MIP images. Conventional digital subtraction angiography (DSA) was performed at the same time points, and postoperative revascularization was classified using the Matsushima grading system. Two independent reviewers blinded to DSA and clinical data performed the assessments, and discrepancies were resolved by consensus. Interobserver agreement for the moya-ASPECTS score was excellent, with a weighted kappa of 0.90 (95% CI, 0.85–0.95).

Cerebral Blood Flow Measurement

Cerebral blood flow (CBF) was quantified using ^{123}I-iodoamphetamine single-photon emission computed tomography (IMP-SPECT) before and 6–12 months after surgery. Using the dual table autoradiography method,[11] resting CBF and acetazolamide-challenged CBF were obtained on the same day, and cerebrovascular reserve (CVR) was calculated as the percentage increase from the baseline. Regions of interest were set in bilateral MCA territories.

Statistical Analysis

Associations between the moya-ASPECTS score, Matsushima grade, angiographic changes, and SPECT-derived hemodynamic parameters were examined using Fisher’s exact test, multiple regression analysis,

and modified Poisson regression, as appropriate. Firth's bias-reduced logistic regression was used for the postoperative infarction analysis. Categorical variables are reported as counts (percentages), and continuous variables are reported as medians [interquartile ranges]. Statistical significance was set at $P < 0.05$.

Results

The baseline characteristics of the patients are summarized in Table 1. Of the 45 hemispheres, 43 had ischemic symptoms, including transient ischemic attacks (n = 34) and cerebral infarctions (n = 9). In 11 cases of moyamoya disease, bypass surgery was performed on only one side. In all 11 cases, the non-operated side had stenotic lesions, but was asymptomatic. Suzuki staging was stage 1 (n = 2 hemispheres), stage 2 (n = 11), stage 3 (n = 31), and stage 4 (n = 1), with no cases in stages 5 or 6. Eight hemispheres were treated with indirect bypass only, and 37 were treated with combined revascularization procedures, most of which were direct bypass, EDS, and EGS.

Table 1
Baseline clinical characteristics

Item	Hemisphere (n = 45)
Age, median (IQR)	8 (6, 10)
Male/Female	24/21
quasi-moyamoya	2
Clinical type	
Cerebral infarction	9
TIA	34
asymptomatic	2
Suzuki stage	
1	2
2	11
3	31
4	1
5 and 6	0
Surgery	
Direct bypass	37
EDS	44
EGS	35
EDAS	11

EDS, encephalo-duro synangiosis; EGS, encephalo-galeo synangiosis; EDAS, encephalo-duro-arterio synangiosis, Data are presented per treated hemisphere unless otherwise specified.

The moya-ASPECTS score based on slab MIP images from 3D TOF MRA correlated well with the Matsushima grade from DSA ($P < 0.001$) (Table 2), but the STA and MMA diameter changes were not significantly correlated with the Matsushima grade (data not shown).

Table 2
Comparison between Matsushima grade and cortical neovascular network (moya-ASPECTS) score

	Matsushima grade				
	A	**B**	**C**	**total**	**p-value [a]**
moya-ASPECTS score					< 0.001
0	0	0	0	0	
1	0	1	1	2	
2	1	4	2	7	
3	13	0	0	13	
4	8	3	0	11	
5	10	1	0	11	
6	1	0	0	1	
total	33	9	3	45	

[a] Fisher exact test

In multiple linear regression analysis, there was an increase of 2.27 in resting CBF change for each additional point in the moya-ASPECTS score (95% confidence interval (CI) 0.87–3.67; p = 0.003) (Table 3). The distribution and normality of the residuals of the regression model as well as homoscedasticity were visually checked using diagnostic plots such as residual plots, QQ plots, and scale-location plots to confirm that there were no extreme deviations from the assumptions. The standardized regression coefficients (Table 3) were moya-ASPECTS score (adj) 0.45 [0.17, 0.72] and Matsushima grade (adj) 0.15 [-1.11, 1.42]. A similar analysis indicated no significant relationship between the changes in CVR and the moya-ASPECTS score or Matsushima grade (Table 4). The standardized regression coefficients (Table 4) were moya-ASPECTS score (adj) -0.08 [-0.40, 0.25] and Matsushima grade (adj) -0.41 [-1.73, 0.90]. The correlation between moyamoya vessel regression and the moya-ASPECTS score was significant (risk ratio (RR) 1.33; 95% CI, 1.12–1.58; p = 0.001) (Table 5). Thus, a 1-point increase in the moya-ASPECTS score was associated with a 1.33-fold higher likelihood of moyamoya vessel regression. There were no cases of symptomatic cerebral infarction after surgery, but asymptomatic cerebral infarction on the treatment side in the first postoperative year occurred in three of the 45 hemispheres. Firth's bias-reduced logistic regression analysis showed that the moya-ASPECTS score was useful for predicting postoperative cerebral infarction (odds ratio (OR) 0.14; 95% CI, 0.01–0.70; p = 0.009) (Table 6). Of these cases, 17 underwent bilateral bypass surgery. Nonparametric analysis after the first and second bypass surgery showed no significant differences for moya-ASPECTS scores (3.1 vs 3.5, p = 0.08), CBF changes (2.5 ± 1.5 vs 3.7 ± 1.5 ml/100 g/min., p = 0.40), or CVR changes (15.7 ± 3.2 vs 12.6 ± 3.2%, p = 0.35).

Table 3
Multiple regression analysis of the relationships of CBF change with moya-ASPECTS score and Matsushima grade

moya-ASPECTS score (unadjusted)	**β**	**95% CI**		**p-value**
	2.47	**1.15**	**3.79**	**0.001**
moya-ASPECTS score (adjusted) [a]	2.27	0.87	3.67	0.003
Matsushima grade (unadjusted)	5.12	-1.70	11.94	0.149
Matsushima grade (adjusted) [a]	0.95	-6.87	8.78	0.813
β: regression coefficient; CI: confidence interval				
[a] Adjusted for age, Suzuki grade and pre-CBF value				

Table 4
Multiple regression analysis of relationships of CVR change with moya-ASPECTS score and Matsushima grade

moya-ASPECTS score (unadjusted)	**β**	**95% CI**		**p-value**
	-1.62	**-6.51**	**3.26**	**0.518**
moya-ASPECTS score (adjusted) [a]	-1.25	-6.54	4.05	0.647
Matsushima grade (unadjusted)	-6.30	-30.23	17.62	0.608
Matsushima grade (adjusted) [a]	-8.28	-34.49	17.94	0.540
β, regression coefficient; CI, confidence interval,				
[a] Adjusted for age, Suzuki grade and pre- CVR value				

Table 5
Modified Poisson regression analysis of the relationship between moyamoya vessel regression and moya-ASPECTS score

moya-ASPECTS score (unadjusted)	**RR**	**95% CI**		**p-value**
	1.31	**1.09**	**1.57**	**0.004**
moya-ASPECTS score (adjusted) [a]	1.33	1.12	1.58	0.001
RR, risk ratio; CI, confidence interval				
[a] Adjusted for age.				

Table 6
Firth's Bias-Reduced Logistic Regression analysis of the relationship between postoperative ipsilateral infarction and moya-ASPECTS score

	OR	95%CI		p-value
moya-ASPECTS score (unadjusted)	**0.43**	**0.12**	**1.11**	**0.085**
moya-ASPECTS score (adjusted) [a]	0.14	0.01	0.70	0.009
OR, odds ratio; CI, confidence interval				
[a] Adjusted for age, Suzuki classification				

A representative case is shown in Fig. 2. An 8-year-old girl presented with transient alternate hemiparesis and was diagnosed with moyamoya disease (Suzuki stage 3). The patient first underwent combined bypass surgery on the left side and symptoms improved. DSA and MR scans were performed a year later before bypass surgery on the other side. DSA revealed marked revascularization of the left external carotid artery and regression of the moyamoya vessels. Slab MIP images also showed revascularization and regression of these vessels. The patient was diagnosed with Matsushima grade A, moya-ASPECTS score of 5.

Discussion

This study shows that the moya-ASPECTS score for revascularization after bypass surgery in patients with pediatric Moyamoya disease is highly correlated with the Matsushima grade. Moyamoya vessels regress as revascularization develops, which makes it difficult to fully evaluate cerebral circulation using the moya-ASPECTS score, but the score may still serve as a useful indicator.

Indirect bypass plays an important role in revascularization in patients with moyamoya disease and may be effective in preventing stroke.[1,2] Most pediatric patients with moyamoya disease are treated with combined indirect/direct bypass, but in some cases, especially in infants, direct bypass is difficult due to the small vessel diameters, so indirect bypass is often chosen. Revascularization status after bypass surgery is of concern to bypass surgeons, but assessment can be difficult. Some cases in which direct bypass is not possible are treated with multiple burr holes[12] and some facilities only use indirect bypass to avoid the risk of hyperperfusion,[13] making objective evaluation of revascularization important.

The Matsushima classification is the only clinically accepted method for assessing revascularization, including angiogenesis, by indirect bypass in moyamoya disease. However, this method requires DSA, provides only a rough assessment, and is influenced by the examiner's subjectivity. In contrast, the moya-ASPECTS score was evaluated on a 7-point scale based on slab MIP axial images, which may enable a more objective evaluation of the extent of angiogenesis. The present study showed that the Matsushima classification did not reflect CBF improvement but that the moya-ASPECTS score was correlated with the degree of CBF improvement. The moya-ASPECTS score may complement

Matsushima grading by providing a noninvasive and more granular assessment suitable for repeated follow-up. The moya-ASPECTS score developed in this study can evaluate the regional distribution of cortical collaterals after revascularization and may provide a simple and objective method for postoperative assessment.

Methods for the evaluation of moyamoya disease cases after bypass surgery using MRA[4,5] include the use of MRA MIP images as an alternative to DSA. This approach is somewhat reliable, but MRA MIP images are less objective because of the need for manual contrast by the radiologist when creating the images. In contrast, source or slab MIP images from 3D TOF MRA are highly objective because the bias of the radiologist does not influence image creation.[6,14,15] Therefore, the moya-ASPECTS score based on slab MIP images provides a more objective assessment of neovascularization after bypass surgery.

The natural progression of moyamoya disease has been described as “IC-EC conversion,” indicating a gradual shift of blood supply from the internal carotid artery system to the external carotid artery system through the development of moyamoya angiogenesis as collateral pathways in response to progressive stenosis or occlusion of the terminal internal carotid arteries, as reflected in the Suzuki classification.[16,17] However, data from continuous observation of this process remain scarce.[18] Revascularization surgery may accelerate or facilitate this IC-EC conversion, because surgically induced neovascularization from the external carotid artery system can lead to regression of basal moyamoya vessels, and some patients may also show progression of the contralateral disease stage after unilateral surgery.[4,19] Thus, postoperative hemodynamic changes in moyamoya disease should not be interpreted as a simple additive increase in collateral blood flow, but rather as a complex redistribution of blood supply from the internal carotid artery system to the external carotid artery system. This concept may explain why the moya-ASPECTS score, which reflects cortical neovascularization from the external carotid artery system, was associated with increased resting CBF but not with improvement in CVR. CVR may be influenced not only by the extent of postoperative neovascularization, but also by regression of pre-existing moyamoya vessels, preoperative hemodynamic impairment, peripheral vascular reactivity, and contralateral collateral circulation.

The limitations of this study include the small number of cases and possible subjective scoring of images. The images were evaluated by two reviewers, and discrepancies were resolved by consensus. The score indicates the presence or absence of revascularization in each region but not the extent of neovascularization. Because the slab image is objective, it may be possible to develop an AI-based evaluation to increase objectivity in this assessment. An MR scan is a repeatable examination, and the timing of neovascularization development and regression of moyamoya vessels will become more apparent in the future. In this study, multiple MRI scanners were used, which could affect image quality and consistency and potentially confound moya-ASPECTS score assessments. To avoid this as much as possible, postoperative MR evaluation was performed with the same model and using the same parameters as those used preoperatively, but the MR system differed in nine cases. However, all were evaluated using MR systems of the same field strength (Prisma and Skyra), which were both manufactured by Siemens, and all had the same imaging parameters. Because there is no significant

difference in SNR, an indicator of image quality, between these two MR models,[20] the results for these nine cases can be considered objective. Another limitation is that factors such as contralateral revascularization status and collateral blood flow status may also affect CBF, in addition to neovascularization after bypass surgery. However, the moya-ASPECTS score, which had a near-normal distribution with seven levels, may be superior to the Matsushima classification, in which most cases were judged to be in grade A.

Conclusion

The derived moya-ASPECTS score from slab MIP images obtained using 3D TOF MRA allows a highly objective assessment of neovascularization after bypass surgery in patients with moyamoya disease.

Declarations

Conflict of Interest:

The authors declare that they have no competing interests.

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None

Author Contribution

• Conceptualization: HI, SN (designed the study)• Formal analysis: RK, YS (image data analysis)• Investigation: NF, FO, SN (patient recruitment and surgical procedures)• Writing – Original Draft: HI (prepared the initial manuscript draft)• Writing – Review & Editing: HI, NF, RK, YS, FO, SN (revised the manuscript and approved the final version.)

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Data Availability:

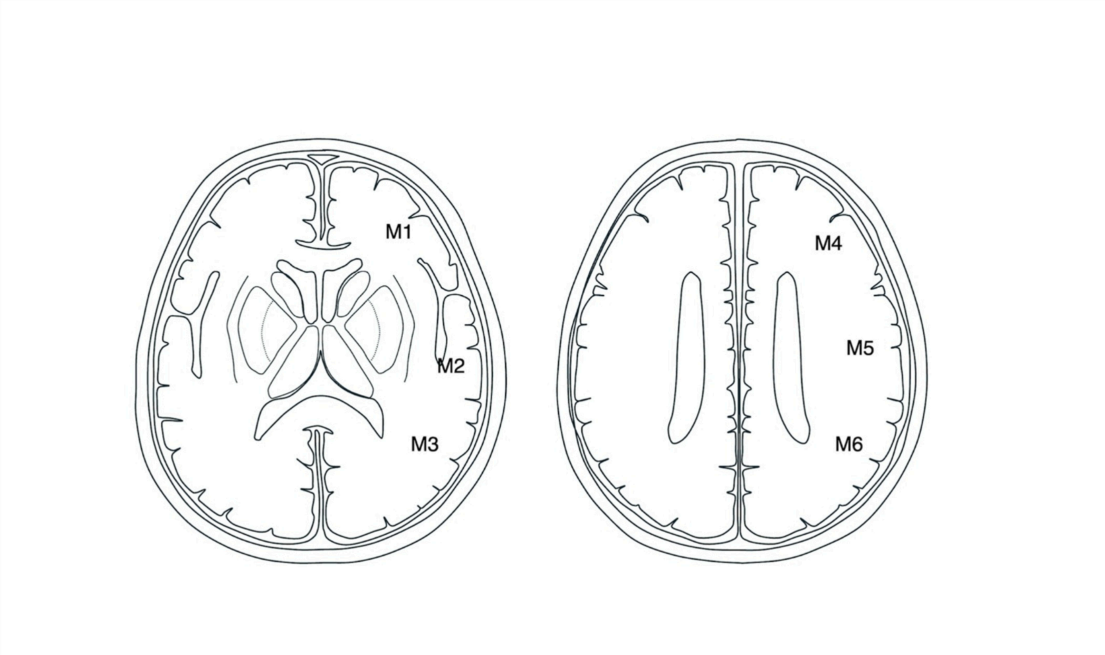
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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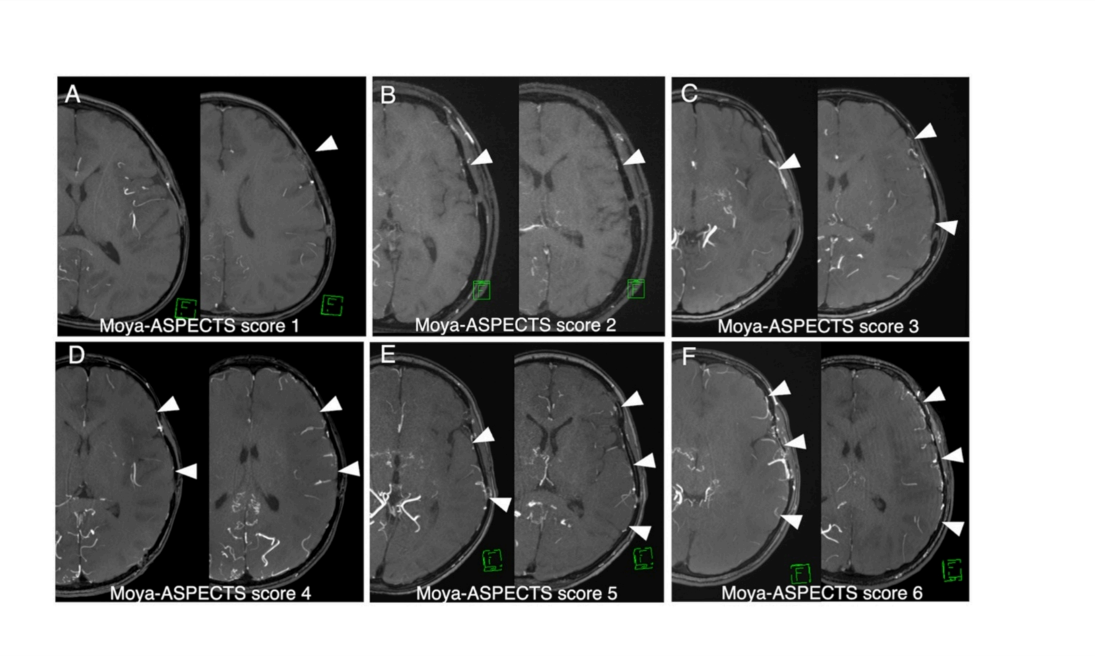
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Figures



1a



1b

Figure 1

1a Cortical areas of the MCA territory divided into 6 regions (M1–M6) according to ASPECTS.

1b Examples of slab MIP images with different moya-ASPECTS scores. A–F correspond to scores of 1–6, respectively. Arrowheads indicate areas of neovascular network.

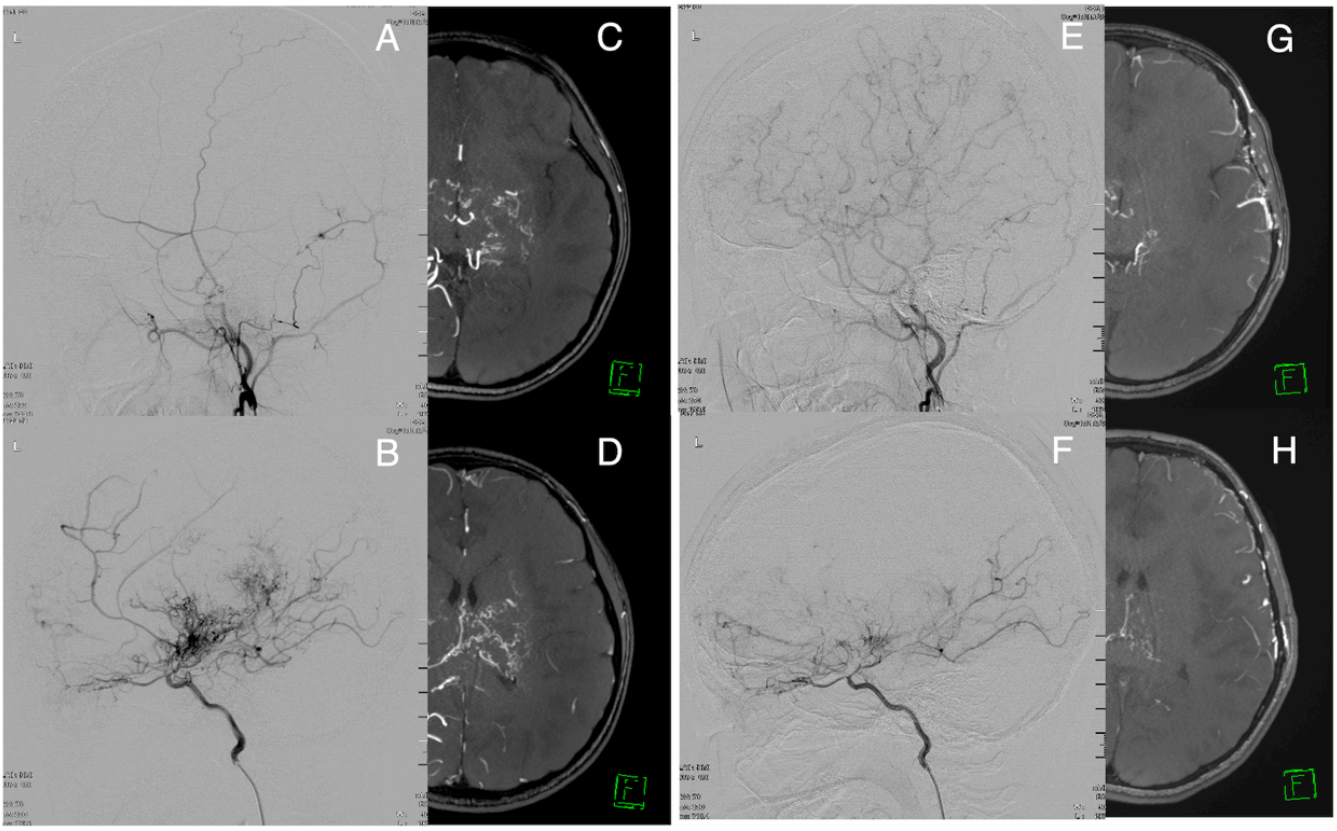


Figure 2

Representative case. (A–D) Preoperative angiograms and slab MIP images: (A) left external carotid angiogram; (B) left internal carotid angiogram; (C, D) slab MIP images. (E–H) At 12 months after bypass surgery: (E) left external carotid angiogram; (F) left internal carotid angiogram; (G, H) slab MIP images.