BRAIN COMMUNICATIONS

Clinical status and evolution in moyamoya: which angiographic findings correlate?

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Moyamoya is a progressive steno-occlusive cerebrovascular pathology of unknown aetiology that usually involves the terminal portions of the internal carotid arteries and/or the proximal portions of the anterior and middle cerebral arteries bilaterally. The preoperative Suzuki staging system and post-operative Matsushima grade are nearly universally used markers of natural history and surgical revascularization results, respectively, but their correlation with clinical and radiographic manifestations of moyamoya has not been systematically evaluated in a large cohort. This study evaluated the strength of correlations between pre- and post-operative angiographic parameters and clinical status among paediatric patients with moyamoya. The participants included 58 patients of mean age 11 years at the time of surgery who underwent bilateral indirect revascularization in the same procedure at Boston Children's Hospital, between January 2010 and December 2015. All included patients had available pre-operative and 1-year post-operative digital subtraction angiography. Clinical data included presenting symptoms, degree of functional incapacity, and peri-operative and long-term complications. Radiographic data included pre-operative Suzuki stage, degree of arterial stenosis, a novel collateral score, the presence of hypovascular territories on digital subtraction angiography, and post-operative Matsushima grade and evolution of stenosis. Chi-squared test and Pearson coefficient were used for correlation studies for categorical variables and Spearman's rho was used for correlation studies for continuous variables. Results showed that Suzuki stage, collateral score and degree of stenosis were insufficient to predict clinical presentation, pre-operative incapacity and radiographic presentation, whereas the presence of hypovascular territories was correlated with all of these. At 1-year follow-up, Matsushima grade was insufficient for predicting peri-operative or long-term complications, nor did it correlate with post-operative incapacity. The presence of hypovascular territories at 1-year follow-up was correlated with the incidence of post-operative ischaemic symptoms.

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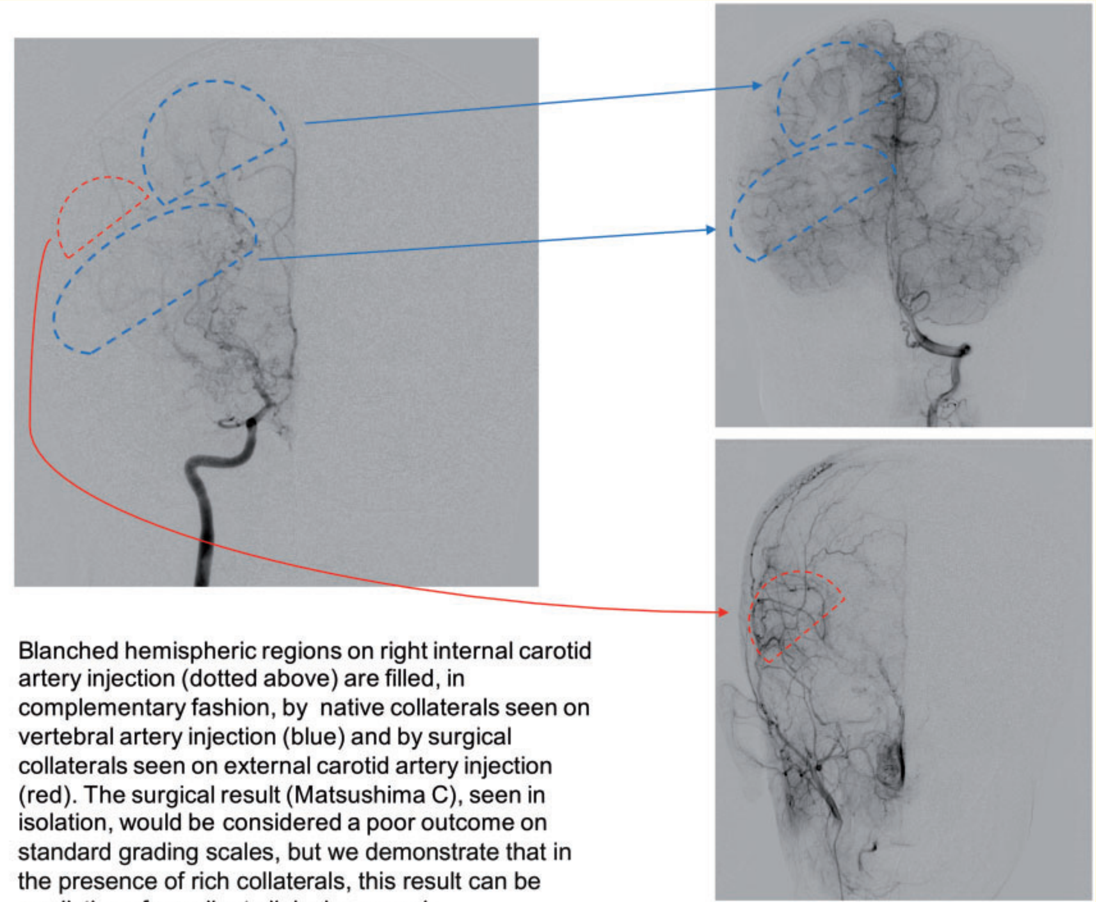
Keywords: angiography; clinical correlation; moyamoya; paediatric

Abbreviations: CA = anterior cereral artery; CCA = common carotid artery; DSA = digital sutaction angiography; ECA = xternal carotid artery; ICA = internal carotid artery; MCA = middle cerebral artery; MM = moyamoya; MMA = middle meningeal artery; mRS = modified Rankin score; OA = ophthalmic artery; PCA = posterior cerebral artery; PCom = posterior communicating artery; RVA = right ertebral artery; TIA = transent ischemic atack

Received April 02, 2019. Revised June 20, 2019. Accepted August 12, 2019. Advance Access publication October 30, 2019

Graphical Abstract



Blanched hemispheric regions on right internal carotid artery injection (dotted above) are filled, in complementary fashion, by native collaterals seen on vertebral artery injection (blue) and by surgical collaterals seen on external carotid artery injection (red). The surgical result (Matsushima C), seen in isolation, would be considered a poor outcome on standard grading scales, but we demonstrate that in the presence of rich collaterals, this result can be predictive of excellent clinical prognosis.

Introduction

Moyamoya cerebral vasculopathy (MM), described for the first time in 1957 by Takeuchi and Shimizu as 'bilateral hypoplasia of the internal carotid arteries' (Takeuchi and Shimizu, 1957), is a progressive, chronic steno-occlusive cerebrovascular pathology of unknown aetiology that usually involves the terminal portions of the internal carotid arteries (ICAs) and/or the proximal portions of the anterior and middle cerebral arteries bilaterally. Less frequent is involvement of the posterior circulation, including the basilar artery and the posterior cerebral arteries. Reduced blood flow in the main arteries of the anterior cerebral circulation leads to the development of compensated collateral circuits by irregular networks of small vessels, called 'moyamoya vessels', deriving from proliferative changes involving perforating branches of the circle of Willis at level of the basal nuclei, on the cortical surface, at the level of the leptomeninges, and by the dural branches of the external carotid artery (Scott and Smith, 2009). Moyamoya is a major cause of ischaemic brain injury in children. There is no current means of reversing the progressive arteriopathy; treatment consists, rather, of surgical revascularization, usually by routing external carotid artery branch(es) to supply the brain, either directly (bypass) or indirectly (synangiosis).

For decades, the angiographic staging system of Suzuki for MM angiopathy has been considered foundational for understanding the temporal profile of the pathology of each patient (Suzuki and Takaku, 1969), quantifying the intrinsic compensatory process of reorganization of cerebral arterial afferents. The appearance of steno-occlusive changes in the region of the ICA terminus and the subsequent development of 'moyamoya vessels' are the characteristic findings in the initial stages (stages 1–3), whereas the compensatory development of transdural and/or transcranial anastomoses from the external carotid artery and the consequent disappearance of the 'moyamoya vessels' represents more advanced stages (4 and 5), followed by the disappearance of the intracranial internal carotid and the regression of the collateral circulation from the external carotid (stage 6, 'burnt out'). This pathophysiological 'internal carotid (ICA)—external carotid (ECA) conversion' is an idealized natural course of patients with MM, both those treated conservatively and surgically. For this reason, the Suzuki angiographic staging, documenting the progressive ICA–ECA conversion, is still considered essential to understand the complex pathology of MM, almost 50 years after its first publication (Fujimura and Tominaga, 2015).

Viewed through a similar ICA-to-ECA prism, the results of surgical revascularization have been expressed for decades using the Matsushima grade (Matsushima and Inaba, 1984). In this system, the percentage of ipsilateral middle cerebral artery (MCA) territory supplied by the ECA-derived collateral circulation through the synangiosis vessels is quantified and stratified into A (>2/3 of the MCA territory), B (1/3–2/3) and C (<1/3).

As a national referral centre, our large paediatric moyamoya patient cohort allowed us to systematically assess the relationship among various radiographic parameters and clinical presentation and outcome. Specifically, we sought to identify correlations between specific angiographic patterns and the clinical status, as well as between specific angiographic patterns and the clinical-radiological evolution after surgical indirect revascularization. We compared our analysis of angiographic patterns as clinical prognosticators with the grading systems widely used in the evaluation of the state of the moyamoya angiopathy (Suzuki staging) and the angiographic results of surgical revascularization (Matsushima grading).

Materials and methods

All work was approved by the Institutional Review Board (IRB) at Boston Children's Hospital. The population of interest included all patients with moyamoya who underwent bilateral indirect revascularization surgery in a single surgical session at the Boston Children's Hospital Cerebrovascular Stroke and Interventions Center (CSIC) between January 2010 and December 2015. The rationale of this inclusion criterion was to limit possible confounding factors due to different progression of the arteriopathy in the same patient between one treated hemisphere and the other hemisphere, either untreated or treated later. The collected data included demographic and pre-operative clinical data, pre-operative digital subtraction angiography (DSA) and MRI, surgical treatment, and clinical and angiographic follow-up.

All patients diagnosed with moyamoya underwent MRI and clinical neurologic and neurosurgical evaluation prior to bilateral indirect revascularization surgery. Each patient underwent pre-operative cerebral DSA to evaluate (i) the status and severity of the moyamoya arteriopathy and (ii) the status of the external carotid branches used for synangiosis. Post-operatively, patients underwent MRA at 6 months and cerebral DSA at 12 months.

Demographic and clinical data

Electronic medical records were reviewed for each patient. Demographic information included age at surgery and sex. Medical histories were reviewed, including information on comorbid pathologies. Data on presenting symptoms were collected, including headache, transient ischaemic attacks (TIAs), ischaemic stroke, seizures, haemorrhag and choreiform movement. Cases of incidental discovery of disease were noted as well.

Operative notes were reviewed in terms of the surgical approach used for each hemisphere. Discharge summaries were reviewed to identify peri-operative complications, including TIAs, ischaemic stroke and surgical site infections.

Post-operative clinical notes were reviewed to identify long-term (>2 weeks post-op) adverse events, which included TIAs, ischaemic stroke, need for further revascularization and development of asymptomatic changes on control MRI. In addition, invalidity status was retrospectively evaluated at presentation and at 1 year follow-up using the modified Rankin Scale (mRS). For the purpose of statistical analysis, mRS was dichotomized as 'good' or 'poor' using two cut-offs: (i) either mRS 0–1 versus 2–6, putting asymptomatic and minimally symptomatic patients on one side versus all others, or (ii) mRS 0–2 versus 3–6, consistent with much literature, in which mRS ≤ 2 with its implication of functional independence is considered to be a good outcome while mRS ≥ 3 is considered poor (Weisscher *et al.*, 2008). Considering that many patients presented a pre-operative mRS higher than 0, we considered not only the absolute final mRS but also ΔmRS, the change between pre- and post-operative mRS for each patient. In this way, patient invalidity was evaluated as improved, stable or worse.

MR evaluation

Ischaemic lesions were evaluated using T2 Spin Echo and T2 FLAIR images in each hemisphere. Lesion location was classified as belonging in territories spanning the anterior cerebral artery (ACA), the MCA, the basal nuclei, the watershed territories between ACA and MCA, or as punctiform white matter hyperintensities.

Angiographic evaluation

All of the patients included in the study population underwent a complete cerebral DSA before surgery and at 1 year post-operatively. The procedures were performed uniformly with a biplane angiography system injecting contrast selectively in the internal and external carotid arteries bilaterally as well as in one vertebral artery, under general anaesthesia.

Pre-operative DSA parameters

At pre-operative DSA, moyamoya arteriopathy at the level of intracranial ICA bifurcations was evaluated using the Suzuki staging for each hemisphere (Suzuki and Takaku, 1969). Additional parameters used to evaluate the severity of the arteriopathy were the grade of stenosis, symmetry of the arteriopathy between hemispheres and the moyamoya involvement of posterior circulation

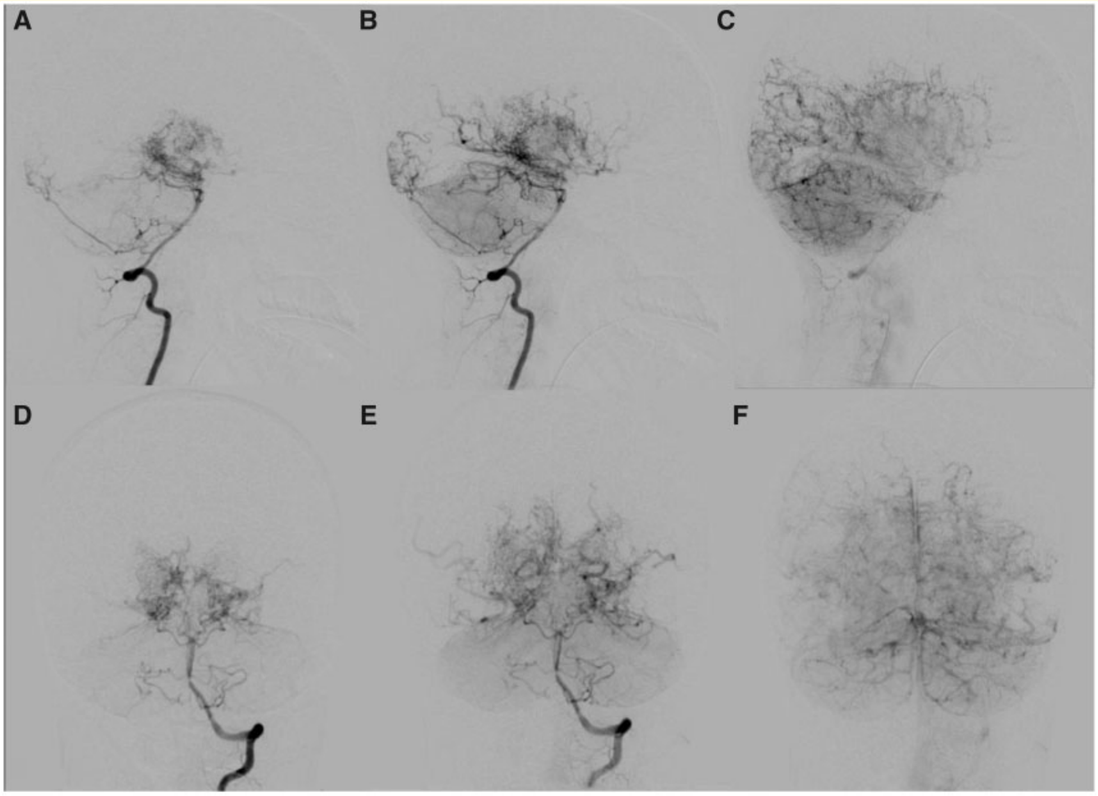


Figure 1 Example of a case of posterior circulation involvement by moyamoya angiopathy, in particular at the level of proximal segment of posterior cerebral arteries bilaterally. Lateral view in early (**A**), intermediate (**B**) and late (**C**) arterial phases. Frontal view in early (**D**), intermediate (**E**) and late (**F**) arterial phases.

(at the level of basilar bifurcation/proximal segments of posterior cerebral arteries; Fig. 1).

Careful attention was given to the evaluation of the collateral circulation directed towards the territories distal to the arterial segment affected by moyamoya angiopathy. The presence of hypovascular areas on the angiograms (i.e. regions containing unopacified wedges in the angiographic capillary phase) was noted as well.

Grade of stenosis of arterial segments affected by moyamoya arteriopathy

Grade of stenosis was classified as: Grade 1, mild-moderate stenosis (<75% luminal narrowing with no impact on flow); Grade 2, severe stenosis with haemodynamic effects; and Grade 3, complete occlusion of the affected segment (Fig. 2). Degree of stenosis was assessed by direct visual inspection, while haemodynamic effect on flow was manifest as delayed flow through the affected segment or slow flow in territories distal to the affected segment.

Collateral circulation

The collaterals were divided on the basis of the different arteries of origin generating flow to the affected territory in each hemisphere, including: the posterior communicating artery (PCom), splenial branches of the PCA, pial cortical branches of the PCA, pial cortical branches of the ACA, perforating vessels of internal carotid bifurcation or proximal (M1) segment of the MCA (lenticulostriates, also described in literature as 'moyamoya vessels'; Suzuki and Takaku, 1969), ethmoidal branches of the ophthalmic artery (OA), and dural branches of middle meningeal artery (MMA). The grading system for each collateral type is shown in Table 1.

Collateral score

The collateral score (ranging from 0 to 12 points) was calculated by summing the scores of all the collateral systems described above for each hemisphere. In addition to assigning a numerical grade of 0–2, collaterals were also dichotomized into 'absent vs. present (any grade)' and 'absent/scarce vs. robust'.

Hypovascular territories at pre-operative DSA

The presence of hypovascular territories on the pre-operative DSA was investigated in each hemisphere by examining the complete arterial supply visualized by the

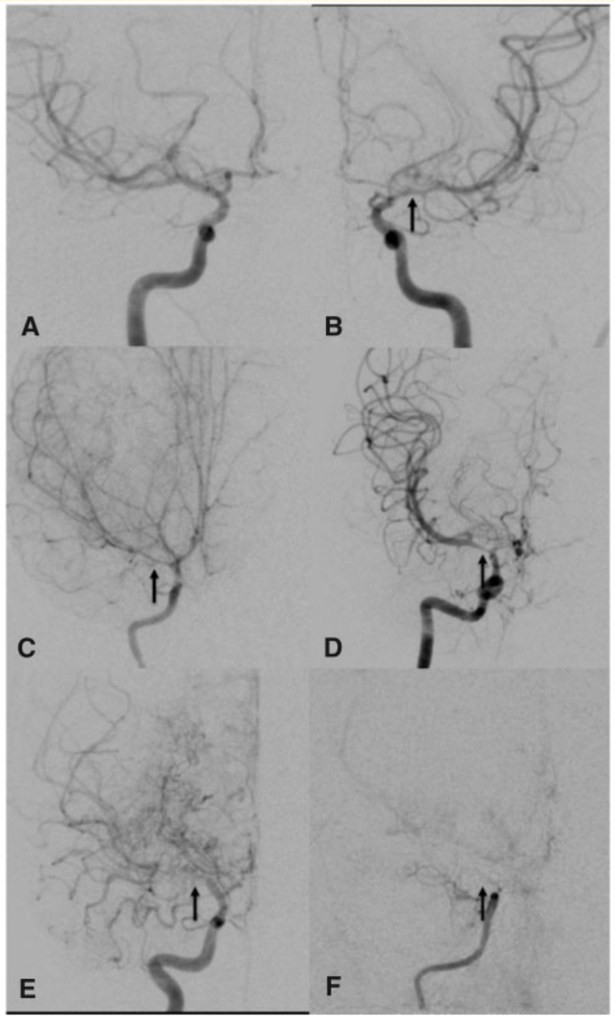


Figure 2 Examples of grades of arterial stenosis in six different patients. (**A**) Mild stenosis; (**B**) moderate stenosis; (C/D) severe stenosis; (E/F) complete occlusion.

injection of contrast in the ICA, ECA (Fig. 3) and the vertebrobasilar system (Fig. 4). Territories that did not opacify in any of the injections, noted by an unopacified wedge on the capillary and early venous phases of the injection, were considered hypovascular. Hypovascular areas included: MCA territory, ACA territory and watershed ACA–MCA territory.

Parameters evaluated at 1 year follow-up DSA after surgical revascularization

At the 1-year DSA, collateral circulation deriving from the ECA through the synangiosis vessels was evaluated according to Matsushima grade (Matsushima and Inaba, 1984), as was the interval progression of the stenosis of the arterial segments affected by moyamoya angiopathy (comparing pre-operative to 1-year post-operative arterial stenosis), as well as the presence of hypovascular territories in every hemisphere 1 year after surgery. For statistical purposes, a 'higher' Matsushima grade is considered worse (i.e. Matsushima grade C).

Statistical analysis

SPSS 20 (IBM Corporation, Armonk, NY, USA) was used for statistical analysis. Crosstabs and Chi-squared test with Pearson's coefficient were calculated for correlations between categorical variables. Spearman's rho was calculated for correlation between categorical or ordinal variables with dichotomic or continuous variables. Unless specifically noted to be inverse, the reported correlations are positive.

Every hemisphere was considered an independent unit for the purposes of statistical testing, and paired sample *t*-test was used to assess for the absence of differences among the means of the variables evaluated in each hemispheres of every patient. For lateralized (hemispheric-centric) variables (i.e. the correlation of Suzuki stage with the presence of ischaemic lesions in the ipsilateral hemisphere), analysis was performed on each hemisphere. For non-lateralized (patient-centric) variables (i.e. the correlation of Suzuki stage and the patient's age) the analysis was repeated for repeated for each hemisphere.

Data availability

Source data for this study, consisting of clinical patient images and clinical notes, are stored in our institution's picture archiving and communication system and electronic medical record, and are protected under HIPAA. Results of analysis of image and clinical data are included in the manuscript and Supplementary materials.

Results

In total, 82 consecutive patients were identified who met initial inclusion criteria. Of these, 15 patients were excluded due to incomplete clinical data or lack of the 1-year follow-up DSA. Of the remaining 67 patients, 9 were excluded due to lack of an available pre-operative DSA. Note that excluded patients typically lacked relevant data due to non-clinical factors such as foreign referrals and insurance refusal; excluded patients did not differ significantly from the study group with regards to male sex (48% versus 38%, $P = 0.41$), age at surgery (10.7 versus 11.4 years, $P = 0.71$) or syndromic moyamoya (39% versus 29%, $P = 0.39$). The remaining 58 patients (36 *f*, 22 *m*) were included in the study cohort (Fig. 5). The mean (±SD) age at surgery was 11.4 ± 6.8 years. In total, 116 cerebral hemispheres were treated by indirect revascularization. Clinical and neuroradiological presentations are summarized in Table 2.

Table 1 Collateral circulation by territory at presentation

Collaterals		Frequency (%)
Posterior communicating artery (PCom)		
Evaluable in 114/116 hemispheres		
Grade 0	Absent	89/114 (78.1%)
Grade 1	Present (Supplementary Fig. 1.1)	25/114 (21.9%)
Splenial branches of PCA		
Evaluable in 115/116 hemispheres		
Grade 0	Absent	36/115 (31.3%)
Grade 1	Present (Supplementary Fig. 1.2)	79/115 (78.7%)
Pial cortical branches of PCA		
Evaluable in 115/116 hemispheres		
Grade 0	Absent (Supplementary Fig. 1.3a)	29/115 (25.2%)
Grade 1	Present, collateral circles limited to the parietal lobe (Supplementary Fig. 1.3b)	65/115 (56.5%)
Grade 2	Present, collateral circles extended to the frontal lobe (Supplementary Fig. 1.3c)	21/115 (8.3%)
Pial cortical branches of ACA		
Evaluable in 115/116 hemispheres		
Grade 0	Absent (Supplementary Fig. 1.4a)	98/115 (85.2%)
Grade 1	Present, collateral circles limited to the supra-insular segment (M4) of MCA (Supplementary Fig. 1.4b)	14/115 (12.2%)
Grade 2	Present, collateral circles extended to the insular segment (M2-M3) of MCA (Supplementary Fig. 1.4c)	3/115 (2.6%)
Perforating branches of ICA terminus and of proximal segment of MCA ('moyamoya vessels')		
Evaluable in 116/116 hemispheres		
Grade 0	Absent (Supplementary Fig. 1.5a)	23/116 (19.8%)
Grade 1	Present, with extension limited to the basal nuclei, directed to the post-stenotic segment of the MCA (Supplementary Fig. 1.5b)	65/116 (56%)
Grade 2	Present, directed to the post-stenotic segment of the MCA and extended within the white matter towards the frontal and parietal cortex (Supplementary Fig. 1.5c)	28/116 (24.2%)
Ethmoidal dural branches of OA		
Evaluable in 116/116 hemispheres		
Grade 0	Absent (Supplementary Fig. 1.6a)	61/116 (52.6%)
Grade 1	Present, with extension limited to the fronto-basal territory (Supplementary Fig. 1.6b)	33/116 (28.4%)
Grade 2	Present, extended beyond the fronto-basal territory (Supplementary Fig. 1.6c)	22/116 (19%)
Dural branches of the ECA		
Valuable in 114/116 hemispheres		
Grade 0	Absent (Supplementary Fig. 1.7a)	61/114 (53.5%)
Grade 1	Present, scarce (Supplementary Fig. 1.7b)	33/114 (29%)
Grade 2	Present, extended beyond 1/3 of the MCA territory (Supplementary Fig. 1.7c)	22/114 (17.5%)

Correlations of pre- and post-operative clinical-radiologic parameters

Results of statistical analysis are summarized in Table 3. More detailed reporting of statistical analysis can be found in the Supplementary materials. The key results are as follows:

i. The degree of arterial stenosis alone was not correlated with specific neurological symptomatology at presentation. Degree of arterial stenosis was weakly correlated with baseline mRS, and the presence of ischaemic changes on pre-operative MRI, and more strongly correlated with the presence of collaterals, both overall collateral score and specific collateral patterns. Moreover, the degree of arterial stenosis alone was not correlated with peri-operative or long-term complications.
ii. Suzuki stage did not correlate with specific clinical presenting symptoms or with baseline mRS, nor was it correlated with peri-operative or long-term complications or with post-operative mRS. Moreover, Suzuki stage at presentation was not correlated with the presence of ischaemic changes on pre-operative MRI, other than in the basal nuclei.
iii. Collateral score at presentation was not correlated with baseline mRS or with ischaemic changes on peri-operative MRI. Collateral score was weakly correlated with risk of peri-operative TIAs.
iv. The presence of hypovascular territories on the pre-operative DSA was correlated with the baseline mRS and the presence of ischaemic changes on pre-operative MRI, and was correlated as well with clinical presentation with specific neurologic symptomatology (TIA, seizures, or choreiform movements rather than headache or asymptomatic presentation). However, the presence of hypovascular territories on pre-operative DSA did not correlate with peri-operative or long-term complications.
v. The presence of posterior circulation involvement was inversely correlated with presentation with headache but positively correlated with presentation with haemorrhage and seizures. In addition, posterior circulation

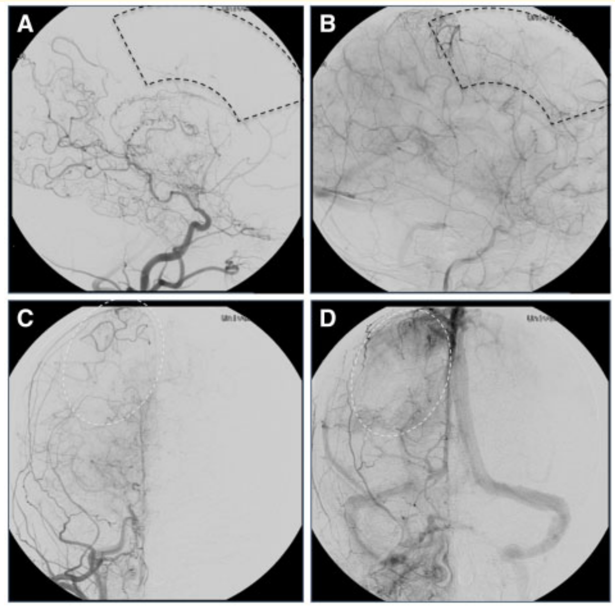


Figure 3 Hypovascularity within the right MCA territory visualized on right common carotid artery (CCA) injection. (Top) Lateral view of (**A**) capillary and (**B**) early venous phases. (Bottom) frontal view of (**C**) capillary and (**D**) early venous phases. Dashed lines denote hypovascular area.

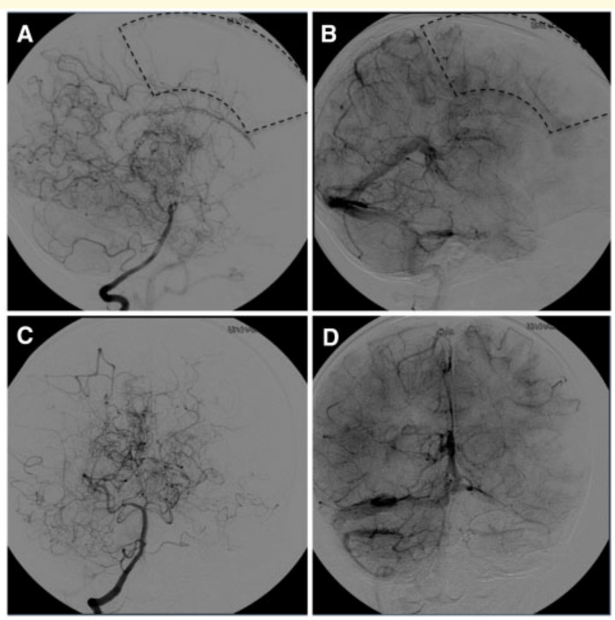


Figure 4 Hypovascularity within the right MCA territory visualized on right vertebral artery (RVA) injection (same patient as Fig. 3). Lateral view of (**A**) capillary and (**B**) early venous phases. (Bottom) Frontal view of (**C**) capillary and (**D**) early venous phases. Dashed lines denote hypovascular area.

involvement was correlated with the presence of ischaemic changes in the MCA distribution on MRI at presentation. It was not, however, correlated with peri-operative and long-term complications.

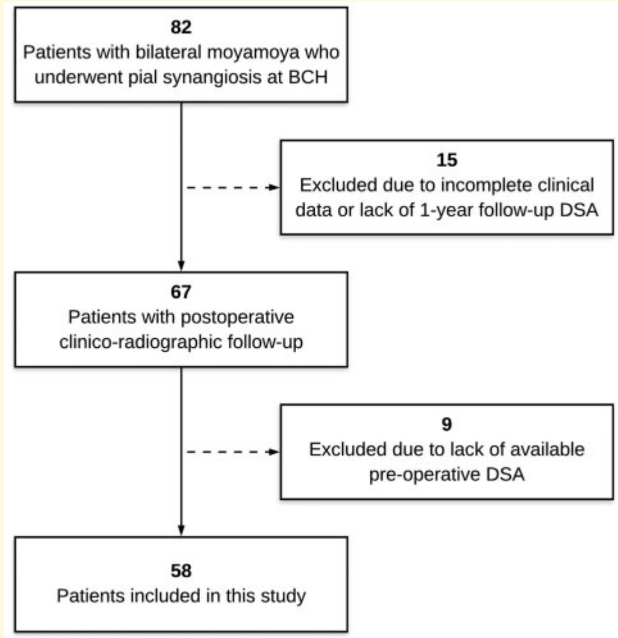


Figure 5 Patient inclusion flowchart.

vi. The Matsushima grade at 1-year DSA was strongly negatively correlated with Suzuki stage and degree of arterial stenosis at presentation, i.e. patients with advanced Suzuki stage at presentation tended to develop rich surgical collaterals (low Matsushima grade).
vii. Matsushima grade at 1 year was strongly correlated with interval progression of stenosis, i.e. patients who develop rich surgical collaterals over the year after surgery tended to have worsened arterial stenosis during that year.
viii. The Matsushima grade at 1-year DSA was strongly negatively correlated with the presence of deep collaterals (from MCA perforators and the OA) and with middle meningeal collaterals, i.e. patients with well-developed deep or MMA collaterals at presentation tended to develop rich surgical collaterals.
ix. However, Matsushima grade was positively correlated with the total collateral score, i.e. patients with a rich network of pial collaterals as well as deep collaterals at presentation (high total collateral score) did not tend to develop rich surgical collaterals (high Matsushima grade). Thus, the presence of rich pial collaterals at baseline predicted poor development of surgical collaterals.
x. The Matsushima grade at 1-year DSA was not correlated with peri-operative and long-term complications and was not correlated with post-operative mRS.
xi. The presence of hypovascular territories at 1-year DSA was strongly correlated with late TIA, but was not correlated with post-operative mRS.

Clinical presentation

The presenting symptom was ischaemic stroke in 23 patients (23/58, 39.7%), associated with signs or symptoms

Table 2 Patient demographics, presentation and post-operative evaluation

Characteristic	Value	
No. of patients	58 (116 hemispheres)	
Female (%)	36 (62.1%)	
Male (%)	22 (37.9%)	
Age at surgery (year)	11.4 ± 6.8 years	
Syndromic[a]	15 (25.9%)	
Down syndrome	5 (8.6%)	
Congenital cardiac anomaly	4 (6.9%)	
Neurofibromatosis type 1	3 (5.1%)	
Sickle cell	2 (3.4%)	
PHACES	1 (1.7%)	
Noonan syndrome	1 (1.7%)	
Primordial dwarfism	1 (1.7%)	
Modified Rankin Score (mRS)	Presentation	1 year follow-up
Median [range]	1 [1, 5]	1 [0, 4]
0	0	28/58 (48.3%)
1	39/58 (67.3%)	21/58 (36.2%)
2	14/58 (24.1%)	5/58 (8.6%)
3	3/58 (5.2%)	2/58 (3.4%)
4	1/58 (1.7%)	2/58 (3.4%)
5	1/58 (1.7%)	0
6	0	0
Pre-operative Suzuki stage		
1	8/116 (6.9%)	
2	21/116 (18.1%)	
3	34/116 (29.3%)	
4	43/116 (37.1%)	
5	8/116 (6.9%)	
6	2/116 (1.7%)	
Pre-operative severity of stenosis		
1 (Mild-moderate)	13/114 (11.2%)	
2 (Severe)	35/114 (30.2%)	
3 (Complete occlusion)	66/114 (59.6%)	
Hypovascular territories	Presentation	1 year follow-up
ACA	5/114 (4.4%)	3/116 (2.6%)
MCA	6/114 (5.3%)	0
ACA/MCA watershed	6/114 (5.3%)	0
Symmetry of moyamoya		
Symmetric	34/58 (58.6%)	
Asymmetric	24/58 (41.4%)	
Length of clinical follow-up (year)	2.7 ± 1.8 years ($n = 51$)	
Available 1-year DSA	58/58 (100%)	
Post-operative Matsushima grade		
A	68/116 (58.6%)	
B	26/116 (22.4%)	
C	22/116 (19.0%)	
Post-operative progression of stenosis		
Progressed	54/115 (47.0%)	
Stable	61/115 (53.0%)	

Continuous data represented as mean ± SD unless otherwise specified. Categorical data represented as *n* (%).
[a]Some patients presented with more than one condition associated with moyamoya.

such as TIAs, headache and/or seizures (Fig. 6A). In 23 other patients (23/58, 39.7%) who did not present with stroke, the main symptoms were TIAs alone or associated with headache, seizures, recurrent vomiting or choreiform movements. Four cases (4/58, 6.9%) presented with headache alone or associated with choreiform movements of the upper limbs. In one case (1/58, 1.7%), the only symptom was seizures and in another case (1/58, 1.7%) the only symptom was choreiform movements. In two cases (2/58, 3.4%), the onset was characterized by a cerebral haemorrhage located in the basal nuclei. In four asymptomatic cases (4/58, 6.9%), the diagnosis of moyamoya arteriopathy was incidental, during the work-up of other concomitant pathologies. The median mRS at presentation was 1 (range 1–5; Fig. 6B).

In 15 patients (15/58; 25.9%), moyamoya was present in the context of an associated syndrome or related condition, of which Down syndrome was most common (5/58; 8.6%; Table 2). This relatively high prevalence of moyamoya syndrome is likely due to the exclusion of unilateral cases, which are often idiopathic in aetiology. In our cohort, syndromic patients did not differ from the non-syndromic patients in any major category listed in Table 2 other than Suzuki stage, with syndromic patients tending to exhibit more advanced stenosis of the ICAs (higher Suzuki stage) at the time of pre-operative work-up.

Neuroradiological presentation

Pre-operative MRI revealed evidence of ischaemia in 39 (39/58; 67.2%) of patients. Ischaemia was noted in the ACA territory in five hemispheres (5/116, 4.3%), in the MCA territory in 12 hemispheres (12/116, 10.3%), in the basal nuclei in 11 hemispheres (11/116, 9.5%), in the ACA–MCA watershed territories in 21 hemispheres (21/116, 18.1%) and hyperintense spots within the white matter in 27 hemispheres (27/116, 23.3%). Several patients demonstrated ischaemia in multiple territories.

Suzuki stages observed at the pre-operative DSA are reported in Fig. 6C. The grade of stenosis of the segments affected by moyamoya arteriopathy was evaluable in 114 hemispheres (114/116, 98%). The severity of stenosis was mild-moderate (Grade 1) in 13 hemispheres (13/114, 11.2%), severe (with haemodynamic effects, Grade 2) in 35 hemispheres (35/114, 30.2%) and presented with complete occlusion of the affected segment (Grade 3) in 66 hemispheres (66/114, 56.9%). The frequencies of different grades of collateral circulation as a function of vascular territory are reported in Table 1, and overall collateral scores are reported in Fig. 6D.

The presence of hypovascular territories was evaluable on the pre-operative DSA in 57 patients (57/58, 98.3%), or 114 hemispheres (114/116, 98.3%). One patient had their pre-operative DSA performed at another hospital, where only the ICAs and ECAs were injected, not the vertebral arteries. Therefore, no definitive conclusions about hypovascular territories could be drawn for this patient. For the remaining 114 hemispheres, hypovascular territories were identified in 17 hemispheres (17/114, 14.9%): five hemispheres (5/114, 4.4%) demonstrated the hypovascular area within the ACA territory, six hemispheres (6/114, 5.3%) within the MCA territory, and six

Table 3 **Correlations of pre- and post-operative clinical-radiologic parameters**

Category	Factor	Corr. (%)	*P*-value
Grade of stenosis at pre-operative DSA			
Clinical presentation	Grade of contralateral stenosis	69.8%	**<0.001**
Pre-operative invalidity	Absolute baseline mRS	19.7%	0.036
	Dichotomized baseline mRS (<2 versus ≥2)	20.3%	0.031
Ischaemic changes on pre-operative MRI	ACA and ACA-MCA watershed territory	20.8%	0.025
	MCA and basal nuclei territory	24.1%	0.009
Collateral patterns	Collaterals from pial PCA	37.1	**<0.001**
	Collaterals from pial ACA	23.8	0.011
	Collaterals from MCA perforating arteries	49.7	**<0.001**
	Collaterals from OA	32.2	**<0.001**
	Collaterals from MMA	26.2	0.005
Collateral score	Pre-operative collateral score	61.5%	**<0.001**
Peri-operative and long-term complications			n.s.
Suzuki stage at pre-operative DSA			
Clinical presentation			n.s.
Pre-operative invalidity			n.s.
Ischemic changes on pre-operative MRI	Basal nuclei territory	29.8%	0.001
Stenosis at pre-operative DSA	Grade of stenosis	55.3%	**<0.001**
Collateral patterns	Collaterals from PCom	19.1%	0.042
	Collaterals from OA	33.2	**<0.001**
	Collaterals from MMA	53.9%	**<0.001**
Collateral score	Pre-operative collateral score	45.5%	**<0.001**
Hypovascular territories at pre-operative DSA			n.s.
Peri-operative and long-term complications			n.s.
Post-operative invalidity			n.s.
Collateral score at pre-operative DSA			
Clinical presentation	Collateral score (right) and choreiform movement	28.3%	0.031
Pre-operative invalidity			n.s.
Ischaemic changes on pre-operative MRI			n.s.
Peri-operative and long-term complications	Collateral score (left) and peri-operative TIA	31.1%	0.017
Hypovascular territories at pre-operative DSA			
Clinical presentation	Seizure		0.026
	TIA		0.039
	Choreiform movement		0.017
Pre-operative invalidity	Absolute baseline mRS	27.4%	0.003
	Dichotomized baseline mRS (<2 versus ≥2)	27.9%	0.003
Ischaemic changes on pre-operative MRI	ACA territory	36.4%	**<0.001**
	MCA territory	32.1%	**<0.001**
Collateral score			n.s.
Peri-operative and long-term complications			n.s.
Posterior circulation involvement			
Clinical presentation	Headache	−29.3%	0.026
	Cerebral haemorrhage	28.6%	0.030
	Seizure	33.5%	0.010
Pre-operative invalidity			n.s.
Ischaemic changes on pre-operative MRI	Left MCA territory	32.2%	0.014
	Right MCA territory	32.3%	0.013
	Left basal nuclei territory	29.2%	0.026
	Right basal nuclei territory	34.2%	0.009
Collateral patterns	Collaterals from splenial branches of PCA	−53.5%	**<0.001**
	Collaterals from pial PCA	−37.3%	**<0.001**
	Collaterals from MMA	37.7%	**<0.001**
	Collaterals from OA	27.7%	0.003
Peri-operative and long-term complications			n.s.
Matsushima grade at 1-year DSA			
Stenosis at pre-operative DSA	Suzuki stage	−29.6%	0.001
	Grade of stenosis	−24.2%	0.009
Collateral patterns	Collaterals from MCA perforating arteries	−24.2%	0.009
	Collaterals from OA	−37.1%	**<0.001**
	Collaterals from MMA	−45.6%	**<0.001**
Collateral score	Pre-operative collateral score	31.6%	0.001
Angiographic parameters of outcome	Hypovascular territories	0.02%	n.s.
	Progression of stenosis	31.1%	0.001

(continued)

Table 3 Continued

Category	Factor	Corr. (%)	*P*-value
Peri-operative and long-term complications			n.s.
Post-operative invalidity			n.s.
Pre-operative angiographic parameters of outcome (Suzuki stage and hypovascular territory)			
Post-operative angiographic parameters of outcome (Matsushima grade, progression of stenosis, and hypovascular territory)	Suzuki stage and post-operative hypovascular territory	−22.5%	0.015
	Suzuki stage and post-operative Matsushima grade	−29.6&	0.001
	Matsushima grade and progression of stenosis	−31.1%	0.001
Hypovascular territories at 1-year DSA			
Peri-operative and long-term complications	Hypovascular (left) and late TIA	32.1%	0.014
	Hypovascular (right) and late TIA	48.7%	**<0.001**
Post-operative invalidity			n.s.

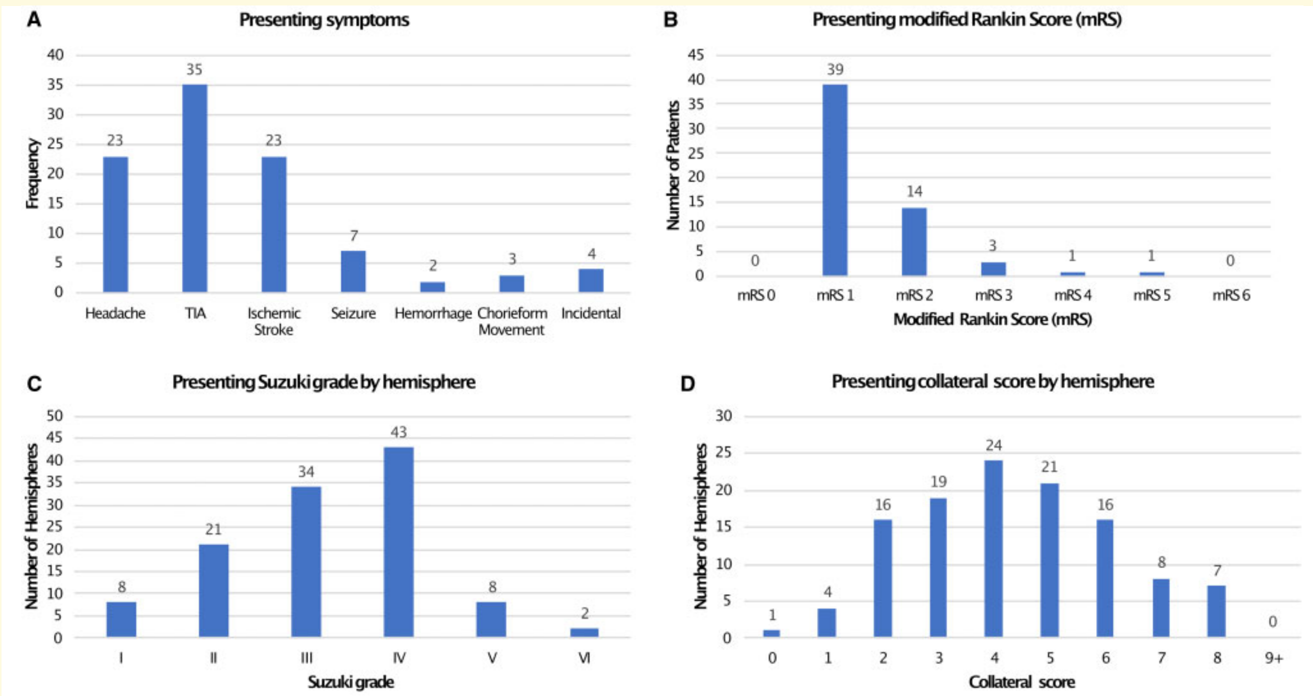


Figure 6 Patient clinical and radiographic characteristics at presentation. (**A**) Presenting symptoms; (**B**) presenting modified Rankin score (mRS); (**C**) presenting Suzuki grade by hemisphere; (**D**) presenting collateral score by hemisphere.

hemispheres (6/114, 5.3%) in an ACA/MCA watershed territory. Moyamoya arteriopathy was bilateral in all patients included in the study, and all patients underwent bilateral revascularization surgery during a single surgical session. The arteriopathy presented with symmetric involvement of both sides in 34 patients (34/58, 58.6%) whereas in the other 24 patients (24/58, 41.4%), the involvement was predominant on one of the two sides. In 14 patients (14/58, 24.1%), the moyamoya arteriopathy also involved the posterior circulation.

Surgical intervention and clinical follow-up

In total, 50 patients underwent bilateral fronto-temporal pial synangiosis; one patient underwent bilateral encephalo-myosynangiosis; two were treated with encephalo-myosynangiosis on one side and fronto-temporal pial synangiosis on the opposite side; five underwent frontal pial synangiosis with pericranial graft on one side and fronto-temporal pial synangiosis on the opposite side.

Peri-operative complications included three ischaemic strokes (3/116, 2.6%, two of which were minor lacunar infarcts), two TIAs (2/116, 1.7%, one of which was associated with intense headache), and three surgical site infections (3/116, 2.6%, two of which were in the same patient).

For 51 patients (102 hemispheres), clinical data for at least 6 months of follow-up were available (mean 2.7 ± 1.8 years; Table 2). One-year follow-up DSA was available for all 58 patients. Patient clinical and radiographic data at 1-year follow-up are summarized in Fig. 7, including Matsushima grade (Fig. 7A) and mRS (Fig. 7B). Median post-operative mRS was 1 (range 0–4).

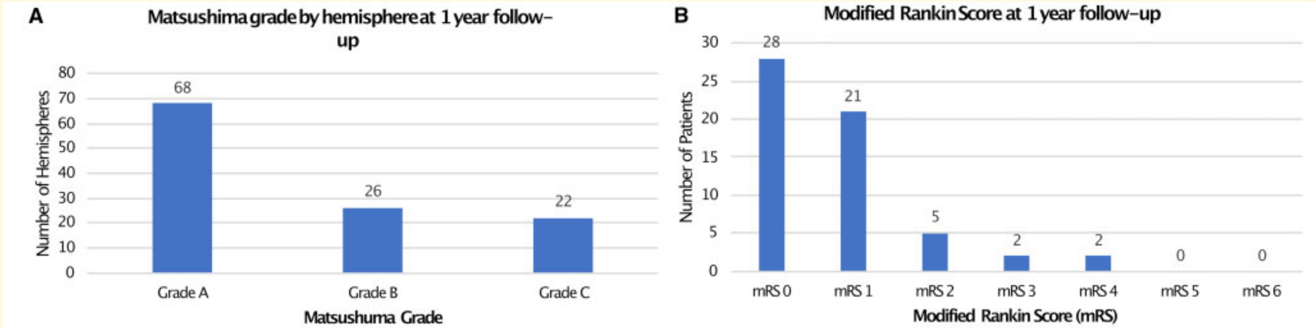


Figure 7 Patient clinical and radiographic characteristics at 1-year follow-up. (**A**) Matshushima grade by hemisphere at 1-year follow-up; (**B**) Modified Rankin score 1-year follow-up.

When compared with the pre-operative mRS scores in the same patients, the post-operative mRS scores improved in 33 cases (33/58, 62.1%), remained stable in 22 cases (22/58, 32.7%) and worsened in three cases (3/58, 5.2%).

Pre- and post-operative DSAs were compared within patients to evaluate progression of stenosis of the segment affected by the moyamoya arteriopathy. In 54 evaluable hemispheres (54/115, 47.0%), the stenosis was noted to have progressed, whereas in the remaining 61 hemispheres (61/115, 53.0%) the grade of stenosis remained stable. At 1-year DSA, hypovascular areas were evident in only three hemispheres (3/116, 2.6%), all located within the ACA territory.

Discussion

Correlations of angiographic patterns with clinico-radiological evolution after indirect surgical revascularization

Despite the wealth of literature utilizing the Suzuki and Matsushima grading systems in quantifying the severity of moyamoya and the efficacy of revascularization, questions remain about their real-world applicability in terms of correlation with clinical presentation and evolution, as borne out by our results. Note that Suzuki staging accounts for only two of the many different vascular systems that are involved in providing collateral circulation to hypoperfused territories: it considers only the perforating branches of the ICA terminus and of the proximal segment of MCA ('moyamoya vessels') and transdural collaterals from the ECA. Since Suzuki staging does not take into account other collateral systems (e.g. leptomeningeal collaterals), it does not offer information about the collateral circulation considered in its entirety. For a given Suzuki stage, we observed instances with robust collateral circulation and other instances with hypovascular territories due to insufficient collaterals. Similarly, hemispheres with different Suzuki stages could present with similar overall global perfusion, due to the balance of different compensating collateral systems.

It is important to note that when the Suzuki staging system was proposed in 1969 it was not devised to evaluate the clinical severity of the patient with moyamoya disease. It was intended rather as a marker of the stage of the intrinsic para-physiologic compensatory reorganization of the cerebral circulation in a process defined as 'internal carotid—external carotid conversion' (Fujimura and Tominaga, 2015).

Matsushima grading was developed to quantify the extension of the area covered by ECA collaterals induced by surgical revascularization. But, as our results demonstrate, in assessing the global perfusion of the hemisphere in a post-operative patient, Matsushima score cannot not be considered in isolation from the angiographic balance.

Correlations between grade of stenosis and clinical-radiologic parameters

In the majority of cases, the intracranial ICA bifurcation exhibited severe stenosis or occlusion on the pre-operative DSA. This is to be expected, as moyamoya is usually clinically silent during its early development and is only diagnosed when cerebral haemodynamic decompensation, due to increasing stenosis and insufficient collateral circulation, induces symptoms.

The correlation between the grade of stenosis and the mRS likely reflects the fact that patients with lower grades of stenosis are unlikely to have developed severe decompensation of cerebral haemodynamics. The analysis demonstrated that the extension of collaterals increased as the grade of stenosis at presentation increased, other than collaterals deriving from the posterior communicating artery (likely because the inflow from the latter is proximal to or included in the segments affected by moyamoya stenosis, and thus does not increase flow distal to the stenotic segment). The correlation between grade of stenosis and 'collateral score', the sum of all the collaterals for each hemisphere, was strong.

The absence of correlation between the grade of stenosis and the peri-operative and long-term complications as well as for the long-term independence status is likely due to the importance of other factors, such as intrinsic and post-operative collaterals in determining complication risk.

Correlations between Suzuki staging and clinical-radiologic parameters

An important result was that the Suzuki stage was not significantly correlated with presenting mRS, nor was it correlated to the clinical outcome in terms of peri-operative and long-term complications and mRS at follow-up. These findings buttress the fact that Suzuki staging does not provide information about the severity of moyamoya in its entirety, and should be used only as an indicator of the level of 'internal carotid—external carotid conversion'. Overall severity of the disease is dependent on other parameters.

Correlations between collateral score and pre- and post-operative clinical-radiologic parameters

Surprisingly, collateral score did not show significant correlation with the clinical picture at presentation as measured by pre-operative mRS and the symptoms at onset, other than a weak correlation with choreiform movements. This non-correlation may be related to the fact that the collateral score alone, not taking in account, i.e. the degree of stenosis, provides limited overall information about the total perfusion to a given hemisphere, as already shown for Suzuki staging. Thus, a patient with a severe stenosis of the ICA bifurcation with scarce collaterals (i.e. low collateral score) will manifest a deficit of perfusion, whereas a patient with the same collateral score but a mild stenosis of the ICA bifurcation would likely have sufficient hemispheric perfusion.

Correlations between hypovascular territories at pre-operative DSA and clinical-radiologic parameters

The limitations of the degree of stenosis, the Suzuki staging and collateral score that have been discussed above may be bypassed by way of another parameter which integrates the haemodynamics effects of reduced flow through stenosed arteries and the compensation provided by collaterals: namely, the presence of hypovascular areas on the late arterial or capillary phases of the DSA. This parameter was correlated with the pre-operative mRS and with symptoms at onset that are likely related to brain hypoperfusion: seizures, TIAs and choreiform movements.

The presence of hypoperfused territories on DSA is better evaluable at the level of the hemispheric surface than within deep territories, likely accounting for the statistically significant correlation between this parameter and the presence of ischaemia within the ACA and MCA territories on pre-operative MRI. The significance of hypoperfusion is consistent with the utility of perfusion imaging (with CT, MRI or nuclear imaging), as has been reported in the work-up of adult moyamoya patients (Ikezaki, 2000).

Correlations between posterior circulation involvement and clinical-radiologic parameters

Our analysis showing that posterior circulation involvement was correlated with a presentation of seizures and haemorrhage and anti-correlated with headache is consistent with the literature (Hishikawa *et al.*, 2013).

In our population, the involvement of posterior circulation was not correlated with peri-operative and long-term complications after surgical revascularization, whereas other studies have reported increased risk of ischaemia in the posterior territory after the revascularization of the MCA territory in patients with PCA involvement (Lee *et al.*, 2015; Kimiwada *et al.*, 2018). Some of this discrepancy may relate to the different populations involved (adult versus paediatric) or the revascularization approach (direct versus indirect bypass).

Correlations between Matsushima grading and clinical-radiologic parameters

As mentioned above, though the Matsushima grading system is commonly used to evaluate the success of revascularization, it did not demonstrate statistically significant correlation with the post-operative outcome parameters, in particular with either absolute mRS or ΔmRS as compared with pre-operative baseline.

As the Suzuki stage and/or the grade of stenosis increased, the Matsushima grade at follow-up was significantly better (i.e. Matsushima grades A or B). Thus patients with more severe moyamoya tended to show broader sprouting of surgical collaterals at the 1-year DSA.

Matsushima grade did not demonstrate any significant correlation with the presence of hypovascular areas at 1-year DSA. Thus, the presence of scarce collaterals deriving from the synangiosis did not necessarily imply the presence of perfusion deficits.

The inverse correlation of the Matsushima grading with the presence of deep collaterals (perforating arteries, ophthalmic arteries) and middle meningeal collaterals is likely related to the fact that such collaterals are indicative of a strong haemodynamic drive for the development of further support, and such patients are more likely to show a broad extension of post-operative synangiosis-derived collaterals (Matsushima A or B). However, the presence of a rich network of pre-operative pial collaterals (high total collateral score) predicted poor sprouting of surgical collaterals from the synangiosis (poor Matsushima grade, i.e. grade C).

Thus, in pathophysiologic terms, the haemodynamic balance between all arterial flow contributions (from the stenosed parent artery, from the intrinsic collaterals and from the synangiosis) must be taken into account in evaluation of post-operative results. Surgical synangiosis seems to induce broader surgical collaterals in cases where the moyamoya angiopathy is more severe, generating major haemodynamic drive, which is then compensated by the activation of more extended collaterals on the cortical surface deriving from the synangiosis (Supplementary Fig. 2). On the contrary, in those cases in which there is less need for additional cerebral blood flow contribution due to a milder stenosis of the ICA bifurcation and to good compensation from the intrinsic pre-operative collaterals, surgical treatment tended to induce less extensive collaterals from the ECA through the synangiosis (Supplementary Fig. 3).

Another interesting result in terms of pathophysiology is the significant inverse correlation between the Matsushima grade and the interval 1-year progression of the stenosis: greater extension of surgical collaterals was associated with progression of stenosis of the affected segment of the artery. Although this may reflect the progressive natural history of moyamoya, it has been hypothesized that this phenomenon may relate to the reduced demand for flow by the distal territory of the affected artery due to the development of post-operative collaterals itself (Supplementary Fig. 4; Houkin *et al.*, 2004).

Although the utility of hypovascular areas on pre-operative DSA has been demonstrated in terms of correlation with presenting mRS, with specific neurologic symptoms, and with the presence of ischaemic lesions on MRI, the limited number of cases with hypovascular areas at 1-year follow-up DSA makes it impossible to draw conclusions about the correlation between this sign and clinical prognosis. Nevertheless, correlation was observed between the presence of hypovascular areas at 1-year DSA and the presence of TIAs at long-term follow-up. Thus, post-operative arteriograms of patients with symptomatology did demonstrate this concrete angiographic finding, suggesting the utility of follow-up DSA (or perhaps perfusion imaging) specifically in that cohort.

Overall clinical characteristics of the cohort and clinical outcome

This paediatric moyamoya patient series, selected with rigid and specific criteria over a period of 5 years, is one of the largest series published by a single centre. The demographic and clinical data regarding clinical presentation are consistent with those of the main published studies (Scott *et al.*, 2004; Kraemer *et al.*, 2008; Bulder *et al.*, 2011; Al-Yassin *et al.*, 2015; Bao *et al.*, 2015; Saarela *et al.*, 2017; Tho-Calvi *et al.*, 2018). In particular, the high number of ischaemic presentations with strokes and TIAs, headaches and, to a lesser extent, seizures, is reflective of the current paediatric moyamoya literature. The association of moyamoya arteriopathy with other syndromes varies among published studies. In our population, moyamoya syndromes were present in 29% of the cases (Table 2).

In terms of overall clinical prognosis in our cohort, patients with a mRS $\leq$2 constituted 93% of the post-operative functional results in our population. When considering metrics of functional independence such as the mRS, it is important to compare the post-operative status with a pre-operative baseline. In this series, within-subjects comparison of post-operative mRS with pre-operative scores showed that over half (62.1%) of patients showed improvement in functional status with a reduction in mRS of at least one point, whereas only a small percentage (5.2%) experienced worsening of functional status during the post-operative follow-up. In the remaining cases (32.7%), the mRS remained stable after treatment.

Considering the need for surgical re-treatments, the overall rate was low (5.8% of previously treated hemispheres). Moreover, in all cases that required secondary surgical revascularization, the second operation was for a territory different (ACA and PCA) than that targeted in the first procedure (MCA territory).

These results confirm that indirect surgical revascularization in the paediatric moyamoya population is not only safe but also efficient, with a high benefit/risk balance.

Limitations

This study is limited by its retrospective nature. The results reflect clinical and radiographic outcomes based on treatment at a single centre by a single surgical team. Although the catchment area for the centre within the USA is broad, the results reflect the specific cohort referred to our centre, including the ethnic, racial and gender distributions of the paediatric moyamoya patient population within the USA.

Conclusions

Suzuki staging for pre-operative evaluation and Matsushima grading for the evaluation of surgical results in moyamoya arteriopathy should be limited to their original purposes: to quantitate the degree of ‘ICA-ECA conversion’ typical of the natural history of the disease, and the results from surgical revascularization, respectively.

These two grading systems did not demonstrate correlation with the clinical findings of our paediatric moyamoya patients on their pre- and post-operative imaging studies. Therefore, Suzuki staging and Matsushima grading should not be used as independent indicators of disease severity or of the success of surgical revascularization.

Imaging correlates of the clinical consequences of moyamoya require an evaluation of the neurovascular balance, taking into consideration all potential arterial contributions to the hemispheric blood flow and recognition of the presence or absence of hypovascular territories. Cerebral vascularization in these patients can be considered a jigsaw puzzle, to which every collateral circle contributes to form the complete picture. An analysis of the collaterals evaluated by the Suzuki staging and the Matsushima grading provides only an incomplete part of this complex puzzle.

Funding

The authors would like to acknowledge the R. Michael Scott Research Endowment Operating Fund, the Ingraham Fund for Neurosurgical Research, the Sage Schermerhorn Chair for Image-Guided Research, the Kids at Heart Fund and the Chae Family Fund for their support of this research.

Competing interests

The authors report no competing interests.

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